FACULTY OF MEDICINE AND HEALTH SCIENCES

HYPOSPADIAS REPAIR IN ADULTS

ARE THE RESULTS DIFFERENT IN COMPARISON WITH CHILDREN? IDENTIFICATION OF PROGNOSTIC FACTORS

Lander Heyerick
Student number: 01306014

Supervisor(s): Prof. dr. Piet Hoebeke, Dr. Anne-Françoise Spinoit

A dissertation submitted to Ghent University in partial fulfilment of the requirements for the degree of Master of Medicine in Medicine

Academic year: 2017 – 2018

GHENT UNIVERSITY

Preface

This dissertation is a result of a prosperous collaboration between Prof. dr. Piet Hoebeke, Dr. Anne-Françoise Spinoit and myself. For the last year and a half, I got the opportunity to enrich myself in a very fascinating discipline in medicine. Therefore, I would like to thank Prof. dr. Piet Hoebeke to give me the opportunity to conduct research in this field of medicine. Special thanks go to Dr. Anne-Françoise Spinoit: without her, I would not have been able to write this thesis. I could always ask the questions I got, she was willing to invest a lot of time in this research topic, but most of all she were a very pleasant person to work with. I would also like to thank all of the members of 'het Kenniskot': during my research period, they were always able to create an enjoyable environment to work in.

I would also like to thank my parents for creating a safe haven in which I am able to achieve my goals: not only for this dissertation, but for all other aspects of my education, you were always there to support me, to make everything more agreeable for me so that I could focus on my studies. Special thanks go to my girlfriend Lien: I would like to thank her for her tireless support, for her special interest in my research topic and especially for her review of the English language. I am a fortune's favourite to have her by my side.

Last but not least, I would like to thank you, the reader of this dissertation, to deepen yourself into this topic. Congenital penile anomalies form a very interesting field of research with a lot of opportunities. Hypospadias is one of the major prototypes of these anomalies. Although a lot of achievements have already been made in this field of medicine, it remains a hot topic for scientific research in which there is much more to learn and to discover. I hope I will be able to awaken your interest in this topic and I hope that you will enjoy reading this dissertation.

November 2017

Lander Heyerick

Table of contents

Abbreviations

BMG	Buccal mucosa graft
DES	Diethylstilbestrol
DHT	Dihydrotestosterone
DSDs	Disorders of sexual development
EDCs	Endocrine-disrupting chemicals
HCG	Human chorionic gonadotropin
HOPE	Hypospadias Objective Penile Evaluation
HOSE	Hypospadias Objective Scoring Evaluation
ICSI	Intracytoplasmic sperm injection
IIEF	International Index of Erectile Function
IPSS	International Prostate Symptom Score
IUGR	Intra-uterine growth restriction
LUTS	Lower urinary tract symptoms
MAGPI	Meatal advancement and glanuloplasty incorporated
PPS	Penile Perception Score
Q_{max}	Maximum flow rate during micturition evaluated by urinary flow studies
TDS	Testicular dysgenesis syndrome
TIP	Tubularized incised plate
TTP	Time-to-pregnancy

List of figures

List of tables

Abstract

INTRODUCTION: Hypospadias is the most common congenital disorder of the penis affecting up to 1 in 300 male livebirths. A ventrally displaced meatus, corpus spongiosum division and ventral hypoplasia of tissues distal to this division are the three hallmarks of the disorder. Causes of hypospadias are likely to be multifactorial, in which the genetic background of the child, maternal influences and environmental factors play crucial roles. Surgical repair of the defect is the mainstay of treatment. International guidelines recommend to perform surgery between 6 to 18 months of age. There are many different surgical techniques described, but most of them follow the same structure. Although the condition is usually repaired during childhood, sometimes patients present in adulthood: in those patients the condition has never been treated before or they present with complications from previous repair. These are called primary and redo patients, respectively. A lot of research has already focused on outcomes of hypospadias repair during childhood. However, outcomes of reconstructive surgery in adult patients are poorly investigated. Therefore, the aims of this study are to assess outcomes of primary and redo hypospadias surgery in adult patients, to identify prognostic factors, if any, influencing surgical outcomes and to compare the outcomes with those available in the literature for children.

MATERIALS AND METHODS: Adult patients with a diagnosis of hypospadias who had at least one surgery performed after the age of 16 years were recruited retrospectively from the surgical database of the tertiary care centre of the Department of Urology at the University Hospital of Ghent. Clinical history, charts and surgery reports were evaluated for all relevant information available. All surgeries were performed by six urologic surgeons with expertise in hypospadias surgery. Success was defined at the surgery level as the percentage of surgeries which not resulted in complications, and at the initial and final patient level as the percentage of patients who did not develop any complication after their first and last surgery in the tertiary care centre, respectively. Various statistical comparisons were made with various statistical tests and logistic regression analyses were performed to identify prognostic factors for surgical outcome.

RESULTS: 65 patients undergoing a total of 111 surgeries were included. 7 (10.8%) and 58 (89.2%) patients were primary and redo, respectively. The mean age at surgery was 37.4 years. Preoperatively, 177 complications were identified: the most frequently reported ones were urethral stenosis, meatal stenosis, cosmetic complications, urethrocutaneous fistulas, recurrent curvature, urethral diverticulum, glans dehiscence. For 74 (79.3%) surgeries, the patient had functional complaints, while there were cosmetic and sexual complaints in 37

(37.0%) and 15 (18.1%), respectively. 128 surgical techniques were utilised: the most frequently used ones were flap techniques, 1-stage buccal mucosa graft, tubularization techniques, end-to-end anastomotic techniques and advancement techniques. The mean follow-up period was 39.4 months. Surgery level success was 36.4%, initial and final patient level success were 36.5% and 63.9%, respectively. Postoperatively, 108 complications occurred and the most important ones were: urethral stenosis, cosmetic complications, urethral fistulisation, meatal stenosis and hematoma. 43 (45.3%) surgeries were still accompanied with functional complaints, 29 (29.6%) with cosmetic and 17 (20.5%) with sexual complaints. There were very statistically significant differences between the occurrence of pre- and postoperative functional complaints ($p < 0.001$), while this was not the case between pre- and postoperative cosmetic complaints ($p = 0.868$) and between pre- and postoperative sexual complaints ($p = 0.774$). Univariate logistic regression analyses were not able to identify any prognostic factors for developing any postoperative complication, for developing urethral/meatal stenosis or for developing urethrocutaneous fistula.

DISCUSSION: Evaluating outcomes regarding hypospadias surgery remains a challenge because there are no standards of assessment. Still, results seemed inferior to those published in the literature. However, the specific methodologic design of this study, together with the high mean follow-up period and the fact that surgeries were conducted in a tertiary care centre could explain these results. Comparing with earlier published series in primary children for the same care centre, the success rate for adult patients was for some outcome measurements nearly half as good as for paediatric patients. Flap- and graft-assisted procedures are relatively more used in the adult setting than in the paediatric setting, while tubularization techniques and advancement techniques are relatively less used. Stenotic complications are relatively more important findings in adulthood than in childhood, while urethrocutaneous fistulas are relatively less reported. Cosmetic concerns already come along after the first failed surgery during childhood and stay more or less constant in importance throughout adulthood. It is important to note that, in order to determine the real complication rate, it is mandatory to assure long-term follow-up since late complications are not unfrequently seen. Despite the limitations of this study, it was demonstrated that adult patients who need additional repair for hypospadias belong to the most difficult and challenging subgroup of hypospadias patients to treat. There is a demanding need to standardize evaluation of outcomes in hypospadias surgery in order to facilitate comparisons between different surgical techniques, patient groups, care centres and so on. Well-designed prospective studies with standardized approaches to classification, diagnosis, treatment and objective outcome assessment are essential to achieve more evidence based medicine in hypospadias surgery.

Samenvatting

INLEIDING: Hypospadie is de meest voorkomende congenitale aandoening van de penis die tot 1 op 300 van alle levendgeborenen treft. Een naar ventraal verplaatste meatus, splitsing van het corpus spongiosum en ventrale hypoplasie van weefsels die distaal gelegen zijn van deze splitsing vormen de drie karakteristieken van deze aandoening. Hoogstwaarschijnlijk is de oorzaak van hypospadie multifactorieel met cruciale rollen voor het kind met zijn genetische achtergrond, de zwangere moeder en omgevingsfactoren. Chirurgische correctie van de aandoening is het basisprincipe van de behandeling. Internationale richtlijnen raden aan om de aandoening tussen de leeftijd van 6 en 18 maanden te corrigeren. Er zijn veel chirurgische technieken beschreven, hoewel de meeste van hen dezelfde structuur volgen. Desondanks dat men normaliter tijdens de kindertijd corrigeert, kunnen ook volwassenen zich presenteren: ofwel zijn deze patiënten dan nog niet eerder geopereerd ofwel vertonen ze complicaties van vroegere ingrepen, respectievelijk primaire en *redo* patiënten genoemd. Er is reeds veel onderzoek gepubliceerd dat zich focuste op de resultaten van hypospadiecorrectie bij kinderen. De resultaten bij volwassenen zijn echter slechts in geringe mate onderzocht. De doelstellingen van deze studie zijn dan ook te achterhalen wat de resultaten zijn van chirurgie bij volwassen primaire en *redo* hypospadiepatiënten, nagaan of er prognostische factoren zijn die de resultaten beïnvloeden en uiteindelijk het vergelijken van de resultaten van deze studie met de resultaten die reeds beschikbaar zijn in de literatuur voor kinderen.

MATERIALEN EN METHODEN: Volwassen patiënten met de diagnose hypospadie met ten minste één uitgevoerde operatie na de leeftijd van 16 jaar werden retrospectief gerekruteerd vanuit de database van de derde-lijnsvoorziening van de Dienst Urologie in het Universitair Ziekenhuis te Gent. Alle relevante informatie werd uit de patiëntendossiers geëxtraheerd. Alle ingrepen werden uitgevoerd door zes urologische chirurgen met expertise in hypospadie-correctie. Succes werd op het operatieniveau gedefinieerd als het percentage operaties waarbij zich geen postoperatieve complicaties voordeden, terwijl succes op het initiële en uiteindelijke patiëntenniveau gedefinieerd werd als dat percentage van patiënten waarbij na de eerste, respectievelijk laatste operatie in de derde-lijnsvoorziening geen complicaties optraden. Statistische vergelijkingen werden gemaakt met verschillende statistische tests en er werden logistische regressieanalyses uitgevoerd om prognostische factoren te identificeren.

RESULTATEN: 65 patiënten ondergingen in totaal 111 operaties, waarvan er 7 (10,8%) primaire en 58 (89,2%) *redo* patiënten waren. De gemiddelde leeftijd bij operatie bedroeg 37,4 jaar. Er werden 177 preoperatieve complicaties ontdekt: de meest gerapporteerde waren urethrale stenoses, meatale stenoses, cosmetische complicaties, urethrale fistels, recurrente curvatuur, urethrale divertikels en glansdehiscentie. 74 (79,3%) operaties waren geassocieerd

met preoperatieve functionele klachten, 37 (37,0%) met cosmetische klachten en 15 (18,1%) met seksuele klachten. Er werden 128 chirurgische technieken gebruikt. De meest gebruikte waren flaptechnieken, enkelvoudige operaties met buccale mucosale greffe, tubularisatietechnieken, *end-to-end* anastomose-technieken en *advancement* technieken. De gemiddelde follow-up bedroeg 39,4 maanden. Succes op het operatieniveau, op het initiële en uiteindelijke patiëntenniveau bedroegen respectievelijk 36,4%, 36,5% en 63,9%. 108 postoperatieve complicaties werden ontdekt, waarvan de meest gerapporteerde waren: urethrale stenoses, cosmetische complicaties, urethrale fistels, meatale stenoses en hematomen. Na 43 (45,3%) operaties waren er nog altijd functionele klachten aanwezig, na 29 (29,6%) cosmetische en na 17 (20,5%) seksuele klachten. Er was een zeer statistisch significant verschil aanwezig in het aantal patiënten dat preoperatief versus postoperatief klaagde over functionele last ($p < 0,001$). Dit was echter niet het geval voor pre- en postoperatieve cosmetische klachten ($p = 0,868$) en voor pre- en postoperatieve seksuele klachten ($p = 0,774$). Univariate logistische regressieanalyses konden geen prognostische factoren opsporen voor het ontwikkelen van een postoperatieve complicatie, voor het ontwikkelen van urethrale/meatale stenose of voor het ontwikkelen van urethrale fistels.

DISCUSSIE: Evalueren van resultaten inzake hypospadiecorrectie is uitdagend gezien er geen standaarden voorhanden zijn. Desondanks lijken deze resultaten inferieur te zijn aan deze van de literatuur. Het specifieke methodologische design van deze studie, samen met de lange gemiddelde follow-up en het feit dat operaties werden uitgevoerd in een derde-lijnsvoorziening kunnen dit echter verklaren. Vergelijkend met de eerder gepubliceerde resultaten van dit centrum bij primaire kinderen, ziet men dat de resultaten voor sommige uitkomstmaten bij volwassenen slechts half zo goed zijn. Flap- en greffe-procedures worden relatief meer gebruikt bij volwassenen dan bij kinderen, terwijl tubularisatie- en *advancement* technieken minder frequent gebruikt worden. Stenoses komen relatief frequenter voor bij volwassenen terwijl urethrale fistels minder vaak optreden. Cosmetische problemen zijn reeds in belangrijke mate aanwezig na de eerste gefaalde ingreep tijdens de kindertijd en blijven dan min of meer constant in belang doorheen de volwassenheid. Het is belangrijk om op te merken dat een lange termijnfollow-up essentieel is om waarachtige resultaten te achterhalen. Desondanks de beperkingen van deze studie werd er aangetoond dat volwassenen bij wie extra ingrepen vereist zijn wegens hypospadie de meest uitdagende patiënten zijn om te behandelen. Het is noodzakelijk om resultaten meer gestandaardiseerd te rapporteren zodat vergelijkingen met de literatuur makkelijker kunnen plaatsvinden. Prospectieve studies met een gestandaardiseerde aanpak zijn essentieel om meer *evidence based medicine* te vergaren in hypospadiecorrectie.

1. Introduction

1.1. Hypospadias summarized

1.1.1. Definition and epidemiology

Hypospadias is the most common congenital disorder of the penis. In this condition, the ventral side of the penis is to a greater or lesser extent insufficiently developed (i.e. hypoplastic) and leads to the following consequences: 1) instead of opening onto the tip of the glans, the urethra opens somewhere onto the ventral surface of the penis, called the urethral meatus (*Lat: meatus urethra*) (1); 2) somewhat proximal to the meatus, the corpus spongiosum is divided and 3) all ventral tissues distal to this division are hypoplastic, including the part of the urethra between the meatus and the corpus spongiosum division. Glans hypoplasia distally to the ectopic meatus is represented by the presence of a glans groove (see further). Taken together, these three hallmarks form a triangular defect (2-4). Often associated findings in patients with hypospadias include chordee, a fixed ventral curvature of the penis (2, 5), and dorsal hooded foreskin, a condition in which there is excessive dorsal prepuce while the ventral part is insufficiently developed (6, 7). Hypospadias occurs isolated without other congenital abnormalities or is part of a syndrome in which other organs are also affected. Depending on the anatomical location of the meatus, hypospadias is usually classified in several categories:

1. Anterior or distal hypospadias: the urethral meatus opens ventrally onto the glans, the corona or the subcorona;
2. Middle or penile hypospadias: the urethral meatus is located ventrally in the distal, middle or proximal penile shaft;
3. Posterior or proximal hypospadias: in this case, the urethral meatus is positioned penoscrotal, scrotal or perineal along the ventral surface (fig. 1) (6).

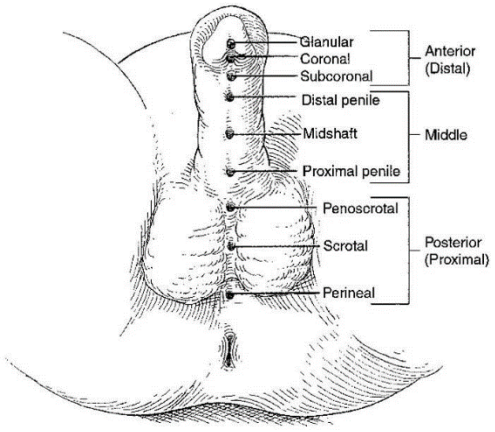


Figure 1. Classification of hypospadias according to meatal location. *Reprinted from Natali et al (8).*

Variations on this classification system exist: for example, distal shaft hypospadias is sometimes classified as anterior hypospadias (9). Although classifying hypospadias according to the position of the meatus provides quick insight into its severity, this sole criterion is not sufficient to assess overall disease severity. Namely, the level of division of the corpus spongiosum, delineating the proximal border of the defect, more adequately reflects the true

severity of this condition and can only be assessed during surgery (2). Based on this perception, new classification systems for hypospadias have been proposed (10, 11).

The prevalence of hypospadias shows major geographical, regional and ethnical differences. The highest mean prevalence is measured in North America and in Europe: these are 34.2 and 19.9 per 10,000 livebirths, respectively. In Asia, some countries (e.g. Turkey) show rates similar to those observed in Europe, while in others (i.e. China) mean rates no higher than 2.3 per 10,000 livebirths are observed. While data are contradictory, suggestions have been made that during the last 30 to 40 years, the prevalence of hypospadias has been rising (12). Possible explanations for this rising trend encompass increased reporting of the disease (13) or the influence of environmental factors (see further).

1.1.2. An embryonic framework of external genital development to elucidate the pathophysiology of hypospadias

The indifferent phase of external genital development

During embryonic development, a cloacal membrane is formed and is surrounded by a pair of cloacal folds that merge ventrally to the genital tubercle (*Lat: tuberculum genitale*). The cloacal membrane is the distal blind ending of the gut tube. Around the sixth week, the urorectal septum (*Lat: septum urorectale*) divides the gut tube and the cloacal membrane with its folds in a ventral and dorsal part: the ventral part of the gut tube becomes the urogenital sinus (*Lat: sinus urogenitalis*) which ends distally in the urogenital membrane (*Lat: membrana urogenitalis*), bordered by the urogenital (or urethral) folds; the dorsal part of the gut tube is now called the anorectal canal which distal ending is the anal membrane (*Lat: membrana analis*), enclosed by the anal folds. A pair of labioscrotal folds or genital swellings is formed bilaterally around the urogenital folds. The bottom of the urogenital sinus disappears as the urogenital membrane breaks down. Up till this stage, the development of male and female is identical. Therefore, this stage is called the ‘indifferent stage’ (fig. 2) (14, 15).

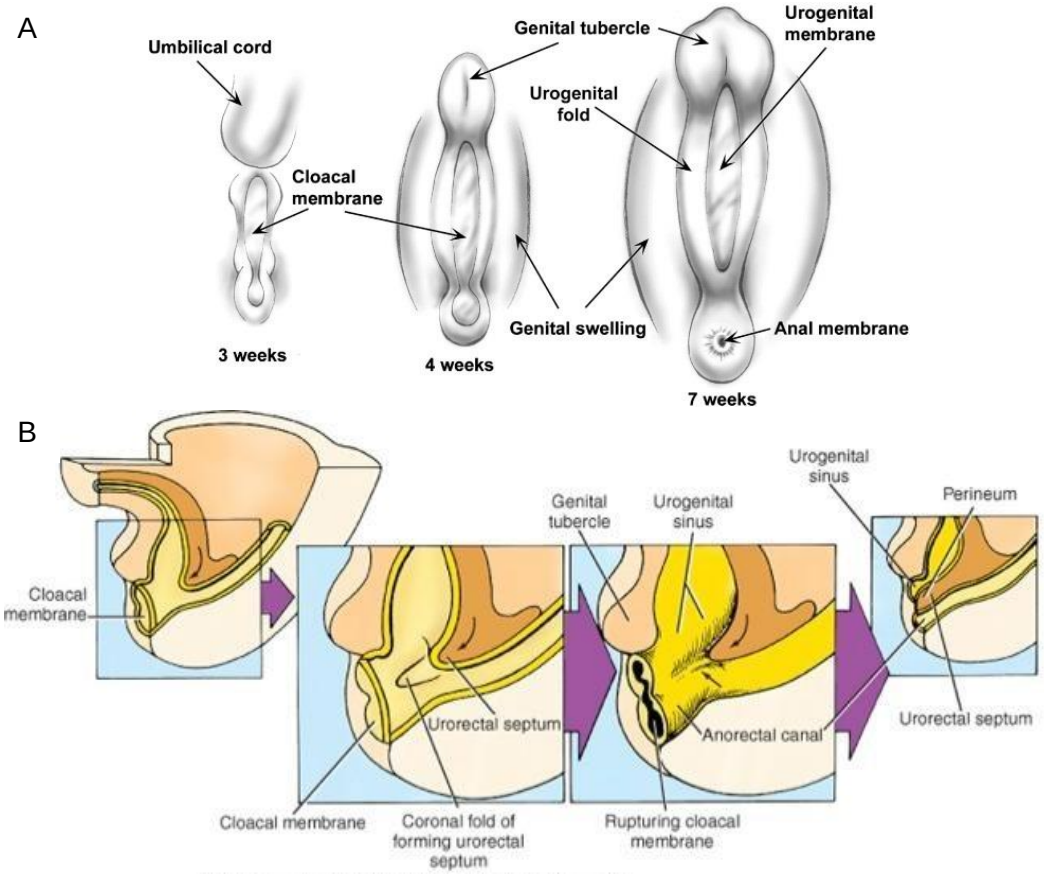


Figure 2. The indifferent stage of genital development. (A) View from inferior. Once the urorectal septum has fully descended, it separates the cloacal membrane and its surrounding cloacal folds in a ventral and dorsal part. (B) View on the caudal migration of the urorectal septum. The gut tube is divided in the urogenital sinus and the anorectal canal because of this decensus. *Adapted from Yamada et al., 2003 (14) (A) and Schoenwolf et al., 2008 (15) (B).*

Male differentiation of the external genitals

From the eighth week, in males, the genital tubercle expands ventrally in response to fetal androgens and shapes the phallus (1, 16). Meanwhile, an endodermal extension of the urogenital sinus also grows ventrally along the inferior surface of the genital tubercle, called the urethral plate. According to the recently developed 'double-zipper' hypothesis (17), a first 'opening zipper' facilitates canalization of the urethral plate, whereby the urethral groove is formed along the course of the urethral plate, together with lateral epithelial edges called urethral folds. This process starts very early during male differentiation, while the urethral plate is not yet formed in the glans penis. It starts proximal from the original position of the urethral meatus near the scrotal folds and then progresses distally over the whole penile shaft up to the beginning of the glans penis. Subsequently, around the middle of the tenth week, a second 'closing zipper' begins to fuse the urethral folds in the midline. In this manner, a sort of bridge is formed over the urethral groove and a tubular structure is created, the tubular urethra. The closing zipper also starts fusing proximal near the perineal segments and then migrates

distally, thus constitutively elongating the tubular urethra. Development of the tubular urethra is finished in the fourteenth week. Meanwhile, the scrotum is created by fusing the labioscrotal folds onto the midline (1, 17, 18) (fig. 3). Multiple theories exist regarding the origin of the part of the urethra located in the glans. According to the most recent theory, the growth of the endodermal urethral plate takes place up to the tip of the penis. The part located in the glans is a solid cord which later on canalizes, thereby forming the glans urethra (1, 19, 20). The stratified squamous epithelium found in the glans urethra would be formed from a differentiation of endodermal cells of the urethral plate (19, 20).

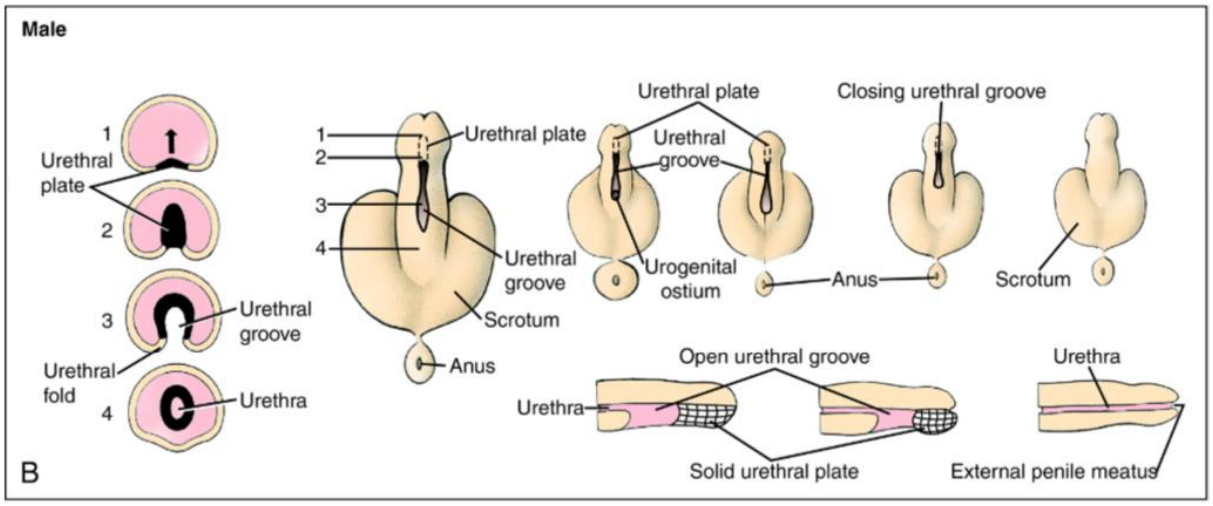


Figure 3. Formation of the male external genitalia. *Reprinted from Schoenwolf et al., 2008 (2).*

In patients with hypospadias, embryonic development of the urethra and its surrounding tissues is incomplete. Any event interfering with urethral development may cause hypospadias, such as events influencing the 1) midline fusion of the urethral folds; 2) growth of the urethral folds; 3) formation of the urethral groove through influencing canalization of the urethral plate and 4) formation of the urethral plate (17). The result is a triangular defect (see above) of which the most proximal aspect of the defect is the corpus spongiosum division. Distally to this division, hypoplastic urethra, not surrounded by corpus spongiosum, is present and ends at the ventrally displaced meatus. The hypoplastic defect is also characterised by a ventrally located glans groove in the glans penis and by a lack of ventral prepuce, explaining the condition of dorsal hooded foreskin (see further). Multiple theories exist regarding the aetiology of chordee (21). Because the urethra is not developed distally to the meatus, urethral plate remains present there and this forms the mainstay of hypospadias repair (see further) (9). The more extensive the underdevelopment, the more proximal the triangular defect is found and the more severe the condition is (1).

1.1.3. Aetiology

The aetiology of hypospadias is mainly unknown, especially in less severe forms, and is likely to be multifactorial in cause (7, 22, 23). However, a lot of research has elucidated important roles for the child with its genetic background, the mother and the environment in explaining the development of this disorder. Most associations are related to insufficient effects of androgen stimulation, thereby causing urethral development to be incomplete.

Hypospadias shows familial clustering, indicating a genetic influence. About 7% of patients with hypospadias have a first, second or third degree relative which is also affected. The concordance rate for monozygotic and dizygotic twins are 27% and 9%, respectively (24). Identified genes implicated in the aetiology of both isolated and syndromic hypospadias are related to penile development, determination of the testis and androgen-synthesis and -action, causing various phenotypes with different penetrance (23, 25). These genes are located on autosomal or sex-chromosomes (7). In such families with established genetic background, it has been demonstrated that in a small proportion monogenetic defects result in the disease (25). Namely posterior hypospadias is more often the result of monogenetic abnormalities (7). However, the majority have a multifactorial or polygenic aetiology (25), which primarily results in anterior hypospadias (7). In comparison with isolated hypospadias, syndromic hypospadias is more often genetic in aetiology and is caused by gene mutations affecting early genital development (23). Also, chromosomal abnormalities are more frequent in syndromic than in isolated hypospadias (13). Some genetic alterations implicating androgen production or -action are associated with male disorders of sexual development (DSDs). DSDs are disorders in which discrepancies exist between chromosomal, gonadal and phenotypical sex (26). They result in severe hypospadias and are often associated with testicular dysgenesis (23). It however should be noted that there is many confusion in the definition of DSD and some argue that ‘intersex’ better defines these discrepancies, while *any* malformation of the penis, including mild isolated hypospadias, is a DSD (27).

Maternal factors are also important in explaining the cause of hypospadias, with an important role for the placenta. Especially placental insufficiency is consistently associated with hypospadias. It is hypothesized that placental insufficiency occurring in the first trimester can lead to both hypospadias and low birth weight, thereby also explaining consistent associations between the latter and hypospadias (7). Because of this insufficiency, intra-uterine growth restriction (IUGR) and inadequate human chorionic gonadotropin (HCG) provision for the fetus arises. HCG is important in facilitating the production of testosterone and dihydrotestosterone (DHT). Because of insufficient production of the latter two, complete virilisation is not possible (7, 22). Maternal hypertension and pre-eclampsia are two conditions which also have been

shown consistently associated with the disorder. Both are associated with placental dysfunction, plausibly caused by compromising uteroplacental perfusion. Additional maternal factors potentially contributing to the aetiology of hypospadias include prolonged time-to-pregnancy (TTP), the use of intracytoplasmic sperm injection (ICSI) for getting pregnant, pre-existing diabetes and use of anti-epileptic drugs (7).

Several findings also support the contribution of environmental factors in explaining hypospadias. As already noted above, the prevalence of hypospadias increased in the last 30 to 40 years (12), an observation which most likely cannot be explained alone by genetics and increased reporting. Moreover, several animal experiments showed various substances like diethylstilbestrol (DES, a synthetic oestrogen), vinclozolin, polychlorinated biphenyls, phthalates and dioxin inducing hypospadias. In humans, it is hypothesized that endocrine-disrupting chemicals (EDCs) are important in causing hypospadias and other genital anomalies like cryptorchidism: these substances, which are for example found in insecticides, fungicides, herbicides and industrial end- and by-products, are similar to endogenous hormones and have the potential to interfere with male genital development. Because of their similarity, most chemicals use the same pathways as endogenous hormones. Xenoestrogens, which are one type of EDCs, have both anti-androgenic and oestrogenic actions (23). Measurement of the anogenital distance has recently been proposed as a predictor of fetal EDC-exposure. In both hypospadias and cryptorchidism-patients, lower mean anogenital distance is observed in comparison with healthy boys (28, 29). However, in humans, no clear causality with any chemical could already be established. Nevertheless, consistent associations between maternal intrauterine DES-exposure and hypospadias have been made (7): in one study, a 21-fold increase in risk of hypospadias was observed with maternal in utero exposure to DES (30). DES also increases the risk of cryptorchidism, decreased sperm count and testicular cancer. The four conditions together are known as testicular dysgenesis syndrome (TDS) (31) and this syndrome covers a fraction of hypospadias patients (7). On the other hand, a population-based case-control study examining occupational exposures to EDCs was not able to show significant associations with hypospadias (31). Also, in most studies, maternal nor paternal exposure to pesticides seems to increase the risk of hypospadias (7).

On top of the above discussed genetic and environmental influences, some authors argue that interactions between both may also contribute to one’s individual risk of developing hypospadias. For example, it has been shown that polymorphisms in the estrogen receptor-gene alter the susceptibility to xenoestrogens, thereby increasing the risk of developing hypospadias (23, 32). In other words, there could be individual susceptibility to environmental factors which is determined by genetics (23). The opposite could also be true, namely that

environmental factors like synthetic oestrogens alter the epigenetic background by influencing DNA-methylation, thereby changing one's susceptibility to develop hypospadias (25).

1.2. Clinical features and diagnosis of hypospadias

Typical clinical features seen in hypospadias may lead to its diagnosis. The parents or the patients themselves may complain about downward deflected urinary stream because of the inappropriate position of the meatus (6, 7). During physical examination, the meatus is found displaced to a more proximal position on the ventral surface of the penis. Sometimes, additional small cavities are seen: the most proximal cavity corresponds to the meatus (5, 13). A typical glans groove on the ventral side of the glans penis may be apparent. There is often a lack of prepuce ventrally and excessive prepuce dorsally, a condition called dorsal hooded foreskin (6, 7) (fig. 4). Chordee is seen in most cases of hypospadias, although it is more common in more severe cases (2, 5). This may be manifest during visual inspection or may be provoked only by inducing an artificial erection during surgery (see further) (6). The megameatus variant of hypospadias is an exception: in this unusual presentation of anterior hypospadias, the prepuce is intact and no chordee is present (34). On the other hand, chordee can also occur without hypospadias (5). In the rare case that the urethral opening is located onto the perineum, a bifid scrotum is seen (35). Penoscrotal transposition, a condition in which the scrotum is positioned superiorly relative to the penis, can also be an associated finding in some very severe proximal cases of hypospadias. There is a complete and an incomplete form, whereby hypospadias is almost exclusively associated with the latter (36).

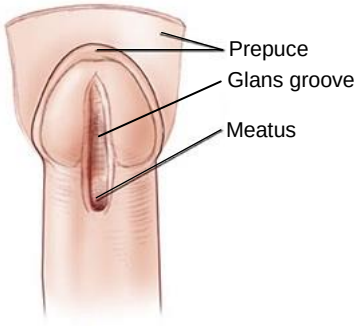


Figure 4. Anatomy of the penis of a patient with hypospadias. The glans groove extends from the meatus up to the distal part of the glans. Note the excessive foreskin dorsally, leading to a dorsal hooded foreskin, and lack of foreskin ventrally. *Adapted from Urology Care Foundation (33).*

Hypospadias may be associated with comorbid congenital anomalies. These are the so called syndromic forms of the condition. Mainly posterior hypospadias presents in a syndromic fashion. The most frequent comorbid conditions observed are cryptorchidism and inguinal hernia. Cryptorchidism, a failure of the testes to descent into the scrotum (7, 13), may be palpated as an 'empty scrotum' during clinical investigation. The testes are (partially) atrophied or are located somewhere on the descending pathway which runs from the abdomen, through the inguinal canal up to the scrotum. If found in the inguinal canal during physical examination, manual traction is not possible to move the testes back into the scrotum. About 8 to 10% of hypospadias patients present with this anomaly. Associated inguinal hernia occurs in 9 to 15% of patients (13).

During physical examination, recognition of the above discussed clinical features in the male neonate make the diagnosis evident (16). However, in case of the megameatus variant it may be possible that the condition is not recognised until the prepuce is retracted or circumcision is performed (37). It is important to describe local findings such as the position, shape and width of the meatus, the size of the penis (9) and the circumference of the glans (3), possible ventral curvature and the presentation of dorsal hooded prepuce and scrotum (37). The width and quality of the urethral plate should also be assessed during visual inspection. The scrotum should also be palpated. If this exhibits unilaterally or bilaterally impalpable testis, or if the patient presents with ambiguous genitalia and/or associated inguinal hernia, active investigation for evidence of a DSD should be performed. These include complete genetic and endocrine investigations (9, 13). Once diagnosis of hypospadias is made, parents should be informed about the condition and its management (37).

1.3. Management of hypospadias

Surgical repair of the defect is the foundation of therapeutic treatment in hypospadias patients. The therapeutic objectives of surgery comprise: 1) correcting the chordee; 2) bringing the neo-meatus to the tip of the glans; 3) gaining acceptable cosmetic appearance; 4) allowing normal functional micturition and 5) achieving satisfying sexual life (9, 38). International guidelines recommend that patients undergo hypospadias repair between 6 to 18 months of age (9). Repairing the defect at this age has several advantages. Firstly, children who are not yet toilet trained, cannot voluntarily delay micturition. Because postoperatively micturition is somewhat painful, older children who are already toilet trained will tend to delay micturition, leading to retention of urine (4) which possibly leads to complications. Secondly, by the age of 18 months, children are aware about their genitalia (37). Repairing the disorder before this age will thus have less psychological consequences. Some authors even advocate repairing between 4 to 6 months of age if the penis is of adequate length and if there are no other medical problems (5, 39). Arguments in favour of repairing at this age include lower complication rates (39), healing occurring more quickly with less profound scarring and recovery from surgery-related stress occurring more easily (5). However, this opinion is not generally accepted: some mention that in severe cases, where far-going dissection of the penis is needed, operating too early could lead to higher blood transfusion risk (38).

There are various surgical techniques which are used for correcting different forms of hypospadias. Some authors even mention that there are as many techniques as there are hypospadias-correcting surgeons. Therefore, it is impossible to gain consensus and develop guidelines about when to use which technique (40). However, the European Association of Urology made recommendations regarding the use of specific techniques according to clinical

presentation (see further) (9). The technique used for an individual patient is ultimately chosen peroperatively and is based on the location of the native meatus (i.e. distal, middle or proximal), penile curvature and penile size, the aspect of the ventral skin before and after deglovement (40), presentation of the urethral plate (3, 9) and level of division of the corpus spongiosum (3).

1.3.1. Preoperative hormonal stimulation

In some patients, preoperative hormonal stimulation with testosterone, DHT or HCG is used to improve surgical outcomes and to reduce complications (41-43). Urologists and surgeons report various indications for hormonal stimulation, including reduced glans circumference, small appearing penis, reduced urethral plate width and proximal hypospadias (41). Based on expert panel consensus, reduced glans circumference should be the reason for starting hormonal stimulation (3). It leads to increases in penile length, glans circumference and neo-vascularisation (42). Because of elongation of the penile shaft, the relative position of the meatus moves distally (5). However, these effects are temporary and tend to regress between 3 to 12 months (3, 43). Topical and intramuscular formulations are available. Use of one or the other does not statistically influence the effect. However, local adverse effects such as genital pigmentation, skin irritation and pubic hair are more frequently reported with topical administration. Although these adverse effects are temporary and disappear after stopping administration, it is suggested that intramuscular therapy may be preferable. There is no consensus about dose-regimen and time of application prior to surgery (42).

Although preoperative hormonal stimulation is being used widely, there is no clear evidence that surgical outcomes are influenced with hormonal stimulation. Moreover, a meta-analysis of complications after surgery suggests a potential relationship between preoperative hormonal therapy and increased complication rates in severe hypospadias (43). More and more urologists and surgeons have concerns regarding the detrimental effects of hormonal stimulation on wound healing (3, 43). Also, the timing of administration is important: if administration occurs too close to surgery, enhanced vascularisation results in increased bleeding risk during surgery (38). Furthermore, patients undergoing therapy less than 3 months prior to surgery are suggested to have higher complication rates than those treated more than 3 months before surgery (44). In summary, preparing the child with hormonal therapy prior to surgery is a controversial technique for reducing complications and improving outcomes (41-43).

1.3.2. General steps of the surgical procedure and different surgical techniques

Every surgical technique is similar in composition and in general consists of preparation of the surgery, orthoplasty, urethroplasty, glanuloplasty and meatoplasty, finalisation of the

procedure and postoperative care. Surgical techniques mainly differ in realizing the urethroplasty (38). In proximal hypospadias repair, some techniques are realised in one stage while others are performed in two stages. The choice for one or another is made during surgery according to the quality of the urethral plate: whenever preservation of this structure is achievable, single-stage repair will be pursued. Generally, if it should be transected, two-stage repairs with the use of grafts provide the solution (40). However, exceptions exist and sometimes one-stage repair grafting is performed in patients with transected urethral plates (see further). Sometimes, transection of the plate is needed to correct very severe chordee. For these cases, two-stage procedures are also required. As will be demonstrated further, vascularised flaps (i.e. a piece of vascularised tissue) are often used in hypospadias surgery with two main purposes: or they are used for realizing the urethroplasty (see flap techniques) or they serve as secondary coverage of the neourethra (45).

Preparation of surgery and orthoplasty

The first step of every surgical procedure consists of placing a traction suture in the glans. Thereafter, a silicone tube catheter is placed in the bladder through the meatus (40). One or more skin incisions are then made in the penile skin according to the technique used, whereafter the skin is degloved (i.e. retraction of the skin to the base of the penis) by dissecting it from the underlying tissue (38). During ventral dissection, care should be taken to avoid damaging the urethra (46). In some cases, these techniques are sufficient to perform complete orthoplasty (i.e. correction of the penile curvature) (38, 45). In other cases, fibrous tissue present in the ventral surface needs to be resected. If after doing this significant chordee still persists, dorsal midline plication (e.g. Tuck plication) or transection of the urethral plate is required (38). When the surgeon decides that the urethral plate is of insufficient quality, transecting the plate can result in release of the chordee (40). On the other hand, if the remaining chordee is not too important, dorsal midline plication is achievable. This comprises a longitudinal incision in the albuginea which is then closed transversally (38, 47). At initial investigation and after every step of chordee correction, an artificial erection test by intracavernous injection of saline should be performed to assess (residual) chordee (38). Full correction of chordee is necessary to allow for successful repair (37).

Urethroplasty, glanuloplasty and meatoplasty

During urethroplasty, the urethra is reconstructed and the meatus is transposed distally to its normal anatomical position. The newly formed urethra is called the neourethra. Subsequently, the glans (i.e. glanuloplasty) and the meatus (i.e. meatoplasty) are reconstructed in order to achieve an as normal as possible appearance. In this section, only the techniques most

frequently used will be discussed. In general, techniques can be divided in advancement, tubularization, flap and graft techniques.

a. Advancement techniques

Advancement techniques describe those techniques in which the meatus is advanced up to the distal part of the glans. The meatal advancement and glanuloplasty incorporated (MAGPI)-technique is the prototype of these techniques.

The MAGPI technique

The MAGPI procedure can be used for repairing glanular and selected coronal hypospadias (5). The general aim of the procedure is to advance the meatus distally onto the glans. It offers good outcomes and reoperation is usually not needed. However, the meatus often looks unnatural because no slit-like appearance can be achieved (40).

The procedure starts by making a subcoronal circumferential incision 6 to 8 mm proximal to the corona of the glans and proximal to the meatus. Then, the penile shaft skin is degloved and if necessary, residual chordee is corrected. Now, a longitudinal incision is made from the dorsal distal edge of the native meatus to the distally localized glans groove (fig. 5: A). This incision transects a transverse bridge of tissue that is often present. Subsequently, the created tissue edges are approximated transversally according to Heineke Mikulicz: the result is that the meatus is advanced distally to the distal end of the glans groove (fig. 5: B). Then, glanuloplasty is performed: first, the glans is incised and the exposed glans edges, called glans wings, are trimmed (fig. 5: C) whereafter they are again approximated to each other (fig. 5: D). This assures a conical appearance of the glans. Subsequently, Byars flaps are created by incising the dorsal hooded foreskin in the midline. In this manner, the skin can be transposed ventrally and sutured to the glans (fig. 6), so that additional tissue is available for healing. Ultimately, the degloved penile shaft skin is again closed (5, 40).

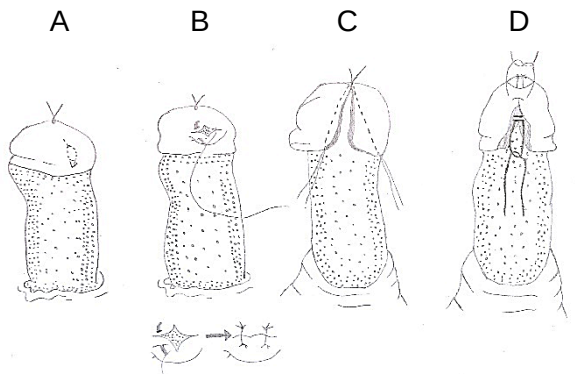


Figure 5. The MAGPI procedure. (A) After skin deglovement, a longitudinal incision from the meatus up to the glans groove is made. (B) The edges are sutured transversally in a Heineke Mickulicz-fashion. (C) The glans is incised and abundant glanular tissue is trimmed. (D) The glans edges are approximated again. *Figure from personal collection.*

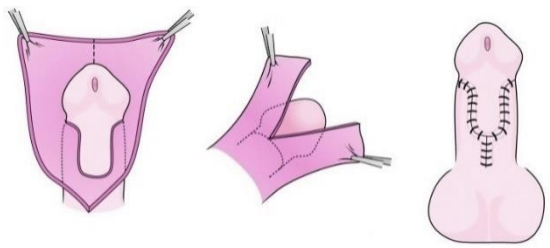


Figure 6. Creation of Byars flaps. When dorsal hooded foreskin is present, this is incised in the midline. In this manner, the skin can be transposed ventrally and sutured to the glans. *Adapted from Jednak et al., 2001 (48).*

b. Tubularization techniques

With tubularization techniques, the urethral plate is tubularized around a catheter in order to construct the neourethra. If the urethral plate is too narrow to be tubularized as such, it needs to be incised to widen it. This is the principle of the tubularized incised plate (TIP) urethroplasty.

The TIP urethroplasty

TIP repair is a surgical technique originally created for correcting distal hypospadias (40). More recently, the technique has been extended to also correct mid shaft and proximal cases (49). However, in proximal cases, remaining penile curvature should be less than 30° after degloving and ventral tissue dissection in order to allow for TIP repair (46). In general, the aim is to form a neourethra by turning the urethral plate into a tube (38). This technique offers excellent satisfaction rates (40).

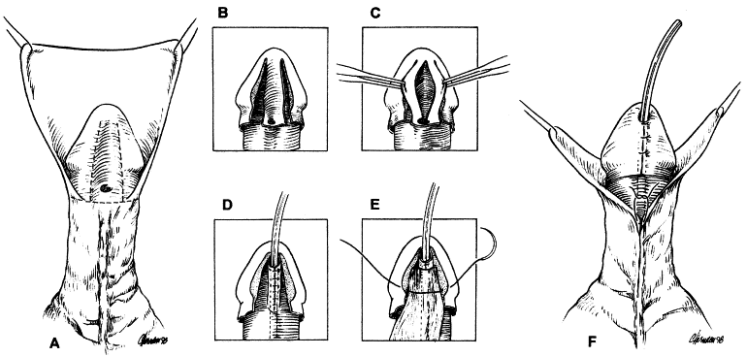


Figure 7. TIP repair. Note that in this figure, the catheter is placed later on in the procedure. (A) Deglovement of the penis is carried out. (B) The urethral plate is separated from the glans wings. (C) The midline relaxing incision through the urethral plate makes tension-free tubularization possible. (D) Tubularization is performed around a catheter. (E) The newly formed neourethra is covered with dartos tissue. (F) glanuloplasty, meatoplasty and skin-closure are performed. *Reprinted from Snodgrass et al., 1999 (50).*

The procedure starts with creating a circumferential subcoronal incision about 1 to 2 mm proximal to the meatus, whereafter the penile skin is degloved (fig. 7: A). Residual chordee can now be corrected. Then, two longitudinal incisions parallel to each other are made in the glans along the lateral margins of the urethral plate, which is located distally to the meatus (fig. 7: B). Tissues lateral from these incisions form the glans wings, medially from them the urethral plate is found. When choosing for TIP repair, the surgeon decided that the urethral plate is too small to be tubularized as such. Therefore, the surgeon creates a midline relaxing incision through the urethral plate, starting from within the meatus up to the end of the urethral plate. However, the edge of the glans should not be incised in order to reduce risk of meatal stenosis. This is the critical step of TIP repair. In this manner, two longitudinal strips of urethral plate are formed whereby the width of the plate increases, making tension-free tubularization possible (fig. 7: C). This is achieved by suturing the two strips to each other in a tubularized fashion. It is important to place the first suture +/- 3 mm proximal to the distal end of the urethral plate in order to create an oval and not rounded meatus. After complete suturing, the neourethra is formed (fig. 7: D). The neourethra is covered by using a dartos flap from the

dorsal or ventral penile shaft skin. If dorsal dartos is used, this first needs to be 'buttonholed' so it can be transposed ventrally through the glans. Ventral dartos is readily prepared to cover the neourethra (fig. 7: E). After doing this, glanuloplasty is performed: this is achieved by approximating the glans wings to each other, starting at the corona and going distally. Eventually, the shaft skin and the meatus are sutured (fig. 7: F). (5, 40, 46).

c. Flap techniques

With flap techniques, the neourethra is formed by tubularization of a flap. This is a piece of tissue that stays connected through its pedicle to the penis itself. Flaps can be made from various kind of tissues but the most important ones are inner preputial skin-tissue and penile skin-tissue. The first mentioned will be further discussed to illustrate these kind of techniques.

Island onlay flap repair

Two key elements of island onlay flap repair include preservation of the urethral plate and the use of a vascularized flap harvested from the dorsal prepuce. The native urethral plate will be used as the dorsal border of the neourethra, while the ventral aspect of it will be formed by the onlay flap. The technique is designed to repair subcoronal to midshaft penile hypospadias (40, 45). First, a circumferential incision is made: dorsally this is carried out 5 to 8 mm proximal to the corona of the glans. However, ventrally, the incision should be continued along the lateral edges of the urethral plate, ending just proximally to the meatus. Thus, according to the location of the meatus, a more or less U-shaped incision is made ventrally. This allows preserving the urethral plate (fig. 8: A). Then, the distal part of the edges of the urethral plate are longitudinally incised bilaterally to the glans. In this manner, laterally to these incisions glans wings are created. Now, skin deglovement is carried out and chordee is corrected (fig. 8: B). Often, after dissection of the ventral surface, hypoplastic spongiosum will be seen near the meatus. In this case, the urethra should be incised proximally up to the level of healthy vascularized spongiosum. Subsequently,

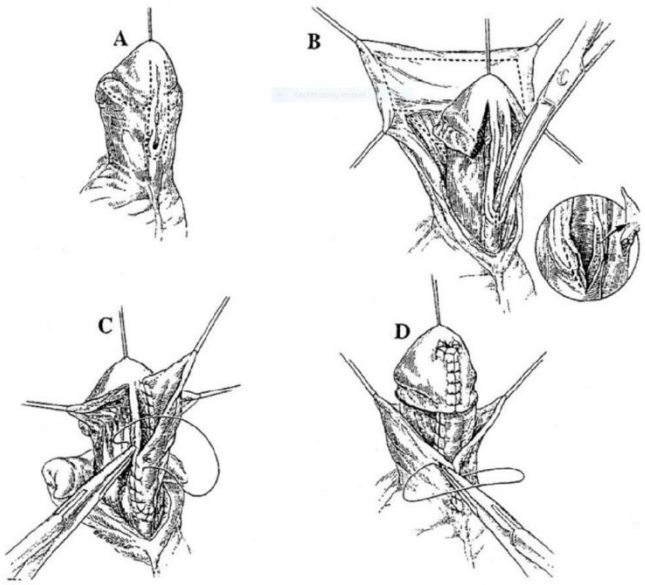


Figure 8. Island onlay flap procedure. (A) A more or less U-shaped incision is carried out circumferentially to preserve the urethral plate. (B) Glans wings are created and skin deglovement is performed. (C) The harvested flap of inner preputial skin is transferred ventrally and sutured to the urethral plate. (D) Eventually, the glans wings are approximated and the neourethra is covered with Byars flaps. *Reprinted from Baskin et al., 2014 (45).*

a rectangular tissue-flap as long as the urethral defect is harvested from the inner layer of the dorsal prepuce, assuring that a 'pedicle' stays attached to the base of the penis. It is important to dissect in a plane between vascularized subcutaneous tissue and outer penile skin, the latter having intrinsic blood supply. Then, the flap is transferred ventrally and is anastomosed to the lateral edges of the urethral plate (fig. 8: C). If the plate is insufficient, then the flap is tubularized. Glanuloplasty is performed by anastomosing the earlier created glans wings and the neourethra is covered with Byars flaps originating from excess outer dorsal preputial skin (5, 40, 45) (fig. 8: D).

Split prepuce in-situ onlay repair

This technique is a modification of the island onlay flap repair. Instead of using the inner prepuce to form the neourethra and the outer preputial skin to cover it as Byars flaps, both the inner and outer prepuce are immediately split vertically. One side is used as an onlay flap, while the other one is used to cover the urethroplasty (45).

Others

There are various other flap techniques which will not be discussed here, including transverse tubularized island flap repair and Koyanagi-Nonomura one stage repair.

d. Graft techniques

When the surgeon decides that the urethral plate needs to be sacrificed and thus transected because it is too unhealthy, free grafts can be used as alternative 'neourethral plate'. The difference with flaps is that no pedicle stays attached to the penis. Unhealthy urethral plates are poorly vascularized and/or unusable for reconstruction due to stricture, fibrosis or urethrocutaneous fistula formation. Grafts are especially needed for proximal hypospadias repair and for hypospadias cripples (see further) (51). When choosing for a graft, mostly a two-stage procedure needs to be implemented. Indeed, it is not recommended to perform urethroplasty on top of a healing graft (45). Moreover, two-staged procedures are less challenging and have a lower tendency of stricture formation. Still, there are some techniques in which grafts are positioned in place and are immediately tubularized, thus in a one-stage procedure. Various grafts are used in clinical practice, like buccal mucosa grafts (BMG), postauricular skin grafts and abdominal skin grafts (51). According to the surgeon, one or the other is preferred more (40).

There are various surgical graft techniques and modifications in hypospadias repair. Generally, in a two-stage procedure, a free graft is harvested during the first stage. This is performed after skin deglovement, resection of chordee tissue and transection of the urethral plate. As already noted, the graft is used to form a neourethral plate. A minimum interval of six months is allowed

for optimal take-up of graft tissue. Then, during the second stage, the newly formed urethral plate is tubularized, thereby creating the neourethra. The neourethra is then covered with dorsal dartos flaps after wrapping them around ventrally. Sometimes, processus vaginalis flaps found near the spermatic cord in the scrotum are used. Eventually, the glans is reconstructed (5, 40, 51).

e. Combination of different techniques

Sometimes, if there is not enough tissue to replace the urethral plate with flaps or grafts alone, a combination of flaps and grafts are used in order to create a neourethra of adequate length (52).

Finalisation of the surgical procedure

As already mentioned while discussing surgical techniques, most of the times a layer of tissue is placed between the constructed neourethra and the penile skin. This is called 'waterproofing' and results in less fistula complications. Tissues which may be utilised include dartos flaps, tunica vaginalis flaps or corpus spongiosum. In case of using the latter, corpus spongiosum adjacent to each side of the urethral plate is mobilized and then approximated to each other in front of the neourethra. After waterproofing, skin coverage is provided according to the technique used. In anterior cases, the prepuce can be reconstructed (i.e. preputioplasty) depending on the wishes of the parents or the patient (38).

Independent of the technique used, the last step of every procedure comprises to check if the silicone tube catheter is still placed in the bladder whereafter the traction suture positioned earlier in the glans is used for securing the catheter (40).

Postoperative care

There is no consensus among authors regarding dressing policies. The rationale for a dressing includes that applying pressure following repair results in less edema, hematoma-formation and infections, while too much pressure can lead to tissue necrosis because of inadequate blood supply (37). However, in two randomized clinical trials no significant difference in surgical outcome and postoperative complications was seen between patients who received postoperative dressing and those who did not (53, 54). The authors suggested that dressings should be excluded from routine postoperative care (53) or may not be indicated for all repair cases (54). Still, expert panel consensus states that immobilizing the penis is important for keeping the wound dry, allowing better healing and reducing postoperative pain (3).

Although it is noted that after the procedure the catheter remains in place, not every author supports the idea to keep the catheter positioned into the bladder in order to achieve urinary diversion. One study noted no significant difference in postoperative complications between

distal hypospadias repair with or without catheter-usage (55). Kraft et al. state that urinary diversion is preferred for proximal and middle hypospadias cases, while its use for distal cases is based more on preference of the surgeon than on proved benefit (5).

When to use which technique?

Table 1 presents a general decision-making approach to decide which technique can be used based on the clinical presentation of the patient. However, it should be noted that only on an individual basis, the right technique can be chosen. Moreover, various surgeon-related factors influence the choice of the technique. An interesting worldwide survey aimed to assess the preferred technique of surgeons according to meatal location. In glanular hypospadias, techniques most widely used are TIP repair and MAGPI. Also in middle hypospadias, TIP is the technique most frequently used. For proximal cases, TIP is not as widely used: the more preferred techniques in this situation are two-staged repairs and to a lesser extent onlay repairs (56).

Table 1. Summary of techniques for hypospadias repair and their indications according to clinical presentation. *Information based on guidelines from the European Association of Urology (9).*

Technique	Distal hypospadias	Proximal hypospadias	
		Urethral plate preserved	Urethral plate transected
MAGPI	✓	X	X
TIP	✓	✓	X
Flap techniques	✓ (subcoronal)	✓	X
Graft techniques	X	X	✓

1.3.3. Complications of hypospadias surgery

As is the case with every surgical procedure, complications can occur. Complications in hypospadias surgery are divided in urethral and non-urethral complications (57). Complications can occur early after surgery or only years after the procedure during puberty or adulthood. It is generally accepted that the surgeon's experience has a lot of influence on the frequency of these complications.

Urethral complications

In general, urethrocutaneous fistulas are the most common complications reported. However, the incidence is reduced since the introduction of waterproofing (38, 58). Because fistulas rarely close spontaneously, surgical management is needed. This can take place from six months on after initial repair in order to allow edema and inflammation to resolve. Different surgical techniques may be approached to deal with this complication according to the position of the fistula (5). Recurrence of fistulas is seen in about 10% of patients (58).

Meatal stenosis is a complication which may occur if the blood supply to the neourethra is compromised. During TIP and MAGPI, not involving the very distal urethral plate in the repair can reduce its occurrence. Also avoiding extreme tight glanuloplasty is important in prevention (5). Once meatal stenosis occurs, this is managed by dilatation or meatoplasty. Stenosis can also occur at the anastomosis between the native and the neourethra or along the entire course of the neourethra and is then called urethral stenosis or urethral stricture. They mainly occur as a long-term complication, especially after graft repair (38, 58, 59), in which erection-induced stretch and trauma on the neourethra eventually leads to fibrosis. Another possible mechanism is that the neourethra is not able to adequately grow together with the penis (59). Hence the importance of long-time follow-up of these patients. Basically, the management is surgical (58).

Urethral diverticula are also well-known complications after hypospadias correction. They may be caused because of distal urethral stenosis, thereby obstructing urinary outflow and proximally leading to ballooning of the urethra. However, they can also arise without obstruction, especially when flap- or graft-based techniques are used (38, 58). In the latter case, avoiding the use of excessive tissue together with adequate tailoring of flaps are essential in its prevention (5). Any excessive tissue needs to be resected in order to treat diverticula (58).

A lot of surgical techniques used in primary hypospadias repair can also be used to manage urethral complications. However, in rare conditions, the urethra has become too extensively stenotic to be able to adequately reconstruct a patent neourethra. In those conditions, the patient has already undergone various failed surgeries in which multiple flaps and grafts are already used. One of the last resort options for those patients involves the construction of a perineal urethrostomy, in which a perineal urethral meatus is created proximally to the stenotic region so that the patient is able to void normally again (60). In this matter, acceptable quality of life is achieved (59).

Non-urethral complications

Early non-urethral complications which may occur after surgery include edema, hematoma, bleeding and infection (58). Glans deformities occurring postoperatively are the result of glans dehiscence, whereby the glans reopens. It is important that glans closure during surgery occurs without tension in order to prevent dehiscence. Another postoperative non-urethral complication includes residual curvature. Surgeon-related causes include not noticing the presence of chordee during surgery or failing to completely correct the chordee. However, penile curvature can also reoccur after complete straightening, many years or even decades after initial repair. One hypothesis explaining its mechanism includes the penile growth spurt during puberty in which the ventral part of the penis and peri-urethral scars grow slower than

other parts of the penis (57). Another plausible mechanism is that the dorsal aspect of the corpora cavernosa, which are normally developed, are more elastic than the ventral side of the penis. Erections, which start occurring from puberty, lead to expanding of the corpora cavernosa but because the ventral side is too rigid, curvature will eventually reappear (61). Again, this states the importance of long-term follow-up.

There are various other non-urethral complications which can occur, most of them mainly resulting in poor cosmetic outcome.

1.4. Hypospadias in adults

Adult patients present with hypospadias in different ways. Firstly, they can be seen into the hospital as a primary case (i.e. without having undergone previous operations for hypospadias). In developed countries, the majority of births are conducted in hospitals and patients more often come into contact with the healthcare system. Because of this, hypospadias is usually early recognised and the patients' parents are properly informed and counselled about the condition and its approach, including the most appropriate age of correcting the defect (62). However, namely in developing countries, lack of awareness about the condition can arise because a lot of births are still performed at home. In addition, factors like ignorance, illiteracy and poverty are important in explaining delayed presentation of this anomaly to the hospital (37, 62, 63). Due to globalization and increasing immigration from developing countries, primary adult cases of hypospadias are nowadays also seen in developed countries.

However, the majority of adult patients consulting the urologist in developed countries have already undergone one or multiple surgical corrections for their hypospadias during childhood. The literature divides this population into two subgroups. Some patients initially have good cosmetic and functional outcome of primary hypospadias repair during childhood, but begin to experience increasing difficulties and problems after multiple years. It is supposed that the neourethra is not able to endure repeated erection-associated stretch and trauma as good as the native urethra, leading to long-term complications in these patients like urethral stenosis (64). On the other hand, there are patients who have undergone multiple failed attempts of repairing hypospadias during child- and adulthood, leaving the penis with significant deformities like scarring of tissues, urethral stenosis, residual curvature, urethrocutaneous fistula and poor cosmesis. Due to far-going anatomic abnormalities, compromised vascularisation caused by scarring and lack of sufficient healthy tissue, these cases are very challenging to reconstruct properly and are often called 'hypospadias cripples' (51, 61, 64, 65).

1.5. Iatrogenic hypospadias

Long-term indwelling urethral catheterisation can lead to several well-known complications like urinary tract infection, mechanical perforation, urethral stenosis and cellular toxicity from the catheter itself. However, the development of iatrogenic hypospadias is a rarely seen complication of long-term catheterisation in clinical practice. One hypothesis explaining its mechanism is that downward pressure of the catheter on the urethra impedes its blood supply, thereby causing ischemic effects which eventually leads to erosions of the penis (66, 67).

There is only limited literature available about this condition, probably because of its rare occurrence. A study of Andrews et al. (66) reported 16 patients over a course of 9 years who needed long-term urethral catheterisation because of spinal cord injury and subsequently developed iatrogenic hypospadias. Remarkably, the time frame between the beginning of catheterisation and the diagnosis of this condition varied from 1 month up to 16 years. One possible explanation for this great range is found in the fact that this condition is only recognised when it is actively searched for. Thus, it is possible that there are a lot more patients with this condition that remain unrecognised (66). Garg et al. (67) made a similar case report in an 80-year old bedridden male patient with bilateral club foot (67).

In general, the same techniques which are used for correcting congenital hypospadias can also be implemented for the management of iatrogenic hypospadias. However, it is clear that prevention of this condition is of uttermost importance. Alternatives for long-term urethral catheterisation like intermittent catheterisation, suprapubic catheterisation or condom drainage should be considered. If long-term indwelling catheterisation is really necessary, attention should be paid to prevent traction on the tubing and to properly secure the catheter to the abdomen or the thigh (66, 67).

1.6. Assessing outcomes after hypospadias repair

As already noted above, two main goals of hypospadias repair encompass achieving a satisfactory cosmetic appearance and a normal functioning penis. Both are equally important in assessing success of repair (68). Since complications of the repair-procedure can result in both negative cosmetic outcomes and limited urinary function, these should always be documented. In assessing postoperative aesthetic appearance, both the perception of the surgeon and the patient should be considered. Important elements determining overall aesthetic result include (but are not limited by) the position and shape of the meatus, the shape of the glans and residual penile curvature during erection (46). Penile function after hypospadias repair is mostly evaluated with urinary flow studies (uroflowmetry), which provide an objective assessment of urethral function according to urinary flow rates and shape of the

flow pattern. Obstructive urinary flow, for example caused by urethral stenosis, results in declining of the maximum flow rate during micturition (Q_{max}) and replacement of a normal bell-shaped flow pattern into a plateau-like, flattened curve (69). Residual volume after micturition should also be assessed with ultrasound. However, it should be noted that since recently, the value of urinary flow studies have been questioned. Indeed, some argue that patients after urethroplasty can show flow curves which appear to be flattened while there is no further evidence for obstruction (3). Additional factors important in considering functional outcomes are asking the patient about the characteristics of his urinary stream (i.e. single projectile stream or spraying stream) and about lower urinary tract symptoms (LUTS). These LUTS are easily investigated with the International Prostate Symptom Score (IPSS): in seven questions, asking about incomplete emptying, frequency, intermittency, urgency, weak urinary stream, hesitancy (straining) and nycturia, the overall severity of LUTS is assessed. Each question grants zero to five points according to the severity of subjective complaints: the maximum amount of 35 points reflects very severe LUTS, while 0 points indicate no LUTS at all (70) (see appendix 1).

A third aspect contributing to overall surgical outcome consists of long-term psychosocial outcomes and sexuality. When evaluating these outcomes, factors like quality of life, penile size and appearance, penile curvature, libido, ejaculation problems, problems during intercourse, overall sexual satisfaction and so on are important to assess. However, these factors are far more challenging to evaluate in comparison with functional and cosmetic outcomes. (46). Moreover, some authors conclude that evaluating long-term sexual function is not useful in determining outcomes of specific surgical techniques (68).

1.7. Hypothesis and aim of the study

Plenty of research has been conducted investigating outcomes of various surgical techniques for hypospadias repair. In the majority of these studies, outcomes of surgery during childhood were assessed. However, outcomes of reconstructive surgery in adult patients are poorly investigated. Nevertheless, they form an important patient group who can present to the hospital with the complications of earlier undergone failed surgery or who present lately and never have been operated before. Due to other anatomical dimensions and possible anatomical deformities from prior surgery, it is possible that adult patients are more or less at risk of developing complications. Therefore, the aim of this study is to assess surgical outcomes of primary and redo hypospadias surgery in adult patients. A second aim is to identify prognostic factors, if any, influencing surgical outcomes. A final aim is to compare the results of this study with the one's available in the literature investigating hypospadias surgery during

childhood, in order to identify if there are differences in the risk of developing complications between both groups.

Having knowledge about surgical outcomes is important in counselling patients who consult for management of their hypospadias, so that they are able to make informed decisions about whether or not to undertake reconstructive surgery. Moreover, by having prognostic factors at one's disposal, complication risk for an individual patient can be estimated, enabling to create a balance of potential benefits and risks of the procedure.

For this dissertation, the student was responsible for the procedure with the Committee of Medical Ethics, for the inclusion of all patients and for the collection, processing and reporting of all data. The co-supervisor of this project was responsible for the designation of all surgeries.

2. Materials and methods

2.1. Patients and surgical procedures

Patients were recruited retrospectively from the surgical database of the tertiary care centre of the Department of Urology at the University Hospital of Ghent with procedure dates between 1st January 1997 and 31st December 2015. All patients included in the analysis accepted an informed consent-form by manner of opting-out (written in Dutch, English or French). The inclusion criteria patients had to meet were: 1) diagnosis of hypospadias and 2) having at least one surgical procedure performed for primary hypospadias repair or postoperative complications after the age of 16 years at the tertiary care centre. Patients were excluded from analysis if there was no clinical chart information available about the preoperative situation. This study was approved by the Committee of Medical Ethics at the University Hospital of Ghent.

Primary patients were defined as patients never having undergone any penile surgery before, while redo patients were defined as patients who ever had undergone any penile surgery at any age. Adult patients were defined as patients aged 16 years and older.

Various surgical procedures were used by various surgeons to correct primary hypospadias or complications from earlier surgeries. These techniques were divided into different groups: 1) flap techniques; 2) graft techniques, including BMG; 3) advancement techniques, including MAGPI, glanular advancement plasty, glanular urethral pull-through, Heineke Mickulicz meatotomy and other non-specific meatoplasties; 4) tubularization techniques, including TIP repair and Thiersch Duplay repair; 5) end-to-end anastomotic repairs, including the Jordan technique and Heineke Mickulicz urethroplasty; 6) 2-stage Bracka; 7) 2-stage Johanson; 8) aesthetic surgeries, including penoplasty and scrotoplasty; 9) Sachse urethrotomy; 10) non-specific techniques for urethrocutaneous fistula closure; 11) perineal urethrostomy; 12) miscellaneous surgeries, including the Tuck plication procedure, surgical abscess drainage and penectomy. All included cases were managed by six urologic surgeons with expertise in hypospadias surgery.

2.2. Data acquisition and analysis

Clinical history, charts and surgery reports were retrospectively evaluated for several patient characteristics. The position of the meatus, both at birth and preoperatively, and the number of previous operations were documented where possible. The clinical charts were also reviewed for functional, aesthetic and sexual complaints as for surgical complications, both pre- and postoperatively. For these complaints, only the final evaluation prior to and after

surgery was documented. A subgroup of patients diagnosed with urethral and/or meatal stenosis also filled in an IPSS, investigating LUTS (70). Lastly, uroflowmetries were reviewed for Q_{max} and voiding volume. In some cases, after uroflowmetry, post-void residual urine was assessed with ultrasound. Uroflowmetry results reflecting the patient's functional status was documented pre- and postoperatively when available. Only uroflowmetries with a voiding volume between 50 and 500 ml were included, unless there was no other uroflowmetry available for that patient.

All complications related to surgical correction were documented and include meatal stenosis, urethral stenosis, urethrocutaneous fistula, urethral diverticulum, chordee, glans dehiscence, cosmetic complications (lichen sclerosans, webbing, scarring, skin defect, wide meatus, necrosis, lymph edema, unaesthetic circumcision, prepuce, glans and/or graft), open urethra, abscess and hematoma. Most of the postoperative complications were diagnosed mainly by physical examination. In suspicion of stenosis, variable combinations of uroflowmetry, retrograde and/or voiding cystourethrography and cystourethroscopy were used to confirm the diagnosis. Obstructive uroflowmetry patterns combined with subjective complaints and/or apparent meatal narrowing was sufficient to diagnose urethral/meatal stenosis. Alternatively, diagnosis was made based on typical findings during cystourethrography or cystourethroscopy. Cystourethrography was also used for confirming the diagnosis of urethral diverticula.

Additional analyses were performed for the most classic complications which occur in hypospadias surgery. These complications were defined as the 'big five' of complications and include meatal/urethral stenosis, urethrocutaneous fistula, urethral diverticulum, chordee and glans dehiscence.

Surgical success was defined on two levels: on the surgery level, surgery was defined as success if the patient did not develop complications during the whole follow-up period available for the given surgery. Temporary complications which spontaneously resolved later or which were treated with non-surgical methods were also documented and hampered surgical success. On the patient level, success was divided into two sublevels: initial patient success and final patient success. Initial patient success encompasses those patients, primary or redo, who did not develop any complications during the whole follow-up period available after their *first* penile surgery at the tertiary care centre. Final patient success is then reached for every patient who did not develop complications anymore after their *last* penile surgery at the tertiary care centre. Based on the classification along the time by Nuininga et al. (71), complications were subdivided in early postoperative (i.e. less than 2 months postoperatively), short-term

(between 2 months and 1 year postoperatively), mid-term (from 1 to 5 years postoperatively) and long-term (more than 5 years postoperatively) postoperative complications.

2.3. Statistics

Information about clinical charts was initially documented with MS® Excel® for Windows, version 2016. Subsequently, statistical analysis was performed with IBM® SPSS® Statistics for Windows, version 24.0 (IBM Corp., Armonk, N.Y., USA). The Wilcoxon matched-pairs signed-ranks test was used for examining differences between pre- and postoperative Q_{max} and between pre- and postoperative IPSS. The Fisher's Exact test was used to investigate differences in complication-rate between primary and redo patients. The McNemar test was used to identify differences between pre- and postoperative functional complaints, between pre- and postoperative cosmetic complaints and between pre- and postoperative sexual complaints. The Phi coefficient was used to identify associations between two nominal variables (i.e. presence/absence of functional, cosmetic or sexual complaints both pre- and postoperatively). Life tables were used to identify the relationship between length of follow-up and occurrence of complications. Logistic regression analyses were performed to identify prognostic factors for developing any postoperative complication, for developing urethral/meatal stenosis and for developing urethrocutaneous fistula. Potentially prognostic factors included in the analysis were: age at surgery, number of penile surgeries undergone before, primary vs redo patient, age at earliest penile surgery, age less than 16 years when undergoing first surgery, presence of cryptorchidism at birth, history of urinary tract infections (cystitis, prostatitis, (orchi-)epididymitis and pyelonephritis), having a preoperative complication, having functional, cosmetic or sexual complaints at preoperative presentation, surgical technique, type of graft used, length of graft used, glanuloplasty and urethroplasty suture (monofilament vs polyfilament), circumcision status, use of an urethral catheter, calibration of the urethral catheter, usage of certain dressings and surgeon. P values of less than 0.05 (two-way) were defined as statistically significant.

3. Results

3.1. General patient's characteristics

68 patients were recruited initially: for 2 patients, there was no preoperative clinical chart information available and 1 patient did not provide informed consent so that eventually 65 patients undergoing a total of 111 surgeries (mean of 1.7 surgeries per patient) were included in this study. The mean age at surgery was 37.4 years (median 36 years) and ranged from 14.6 to 76.5 years. 3 surgeries from 3 patients, operated before the age of 16, were also included because these patients also had at least one surgery after the age of 16. The patient's characteristics are summarized in Table 2. Both iatrogenic hypospadias patients included in this study developed this condition as a result of traumatic catheterisation. One of these patients was a primary patient, while the other one had already undergone surgeries before. 19 (29.2%) out of 65 patients reported a history of urinary tract infections before presentation and 5 (7.7%) more patients developed one or more urinary tract infections during their course at the tertiary care centre. A lot of redo patients had lost count over the number of surgeries they already had undergone before. However, in 47 patients, the amount of surgeries undergone before the first presentation was known: a mean of 3.0 surgeries (median 2.0) were performed before and ranged between 0 and 25. The age at first repair was known for 41 patients: patients were on average 12.2 years old (median 6 years), ranging from 1 to 61.5 years old. Of the 52 patients for which this was known, 43 (82.7%) had already undergone one or more surgeries during childhood, while 9 (17.3%) never had undergone any penile surgery during childhood. Numerous patients had forgotten or even never knew the original location of their meatus. Therefore, these are not reported.

Table 2. Patients' characteristics (n = 65).

	No. of patients, (%)
Type of patient	
Primary	7 (10.8)
Redo	58 (89.2)
Aetiology of hypospadias	
Congenital	63 (96.9)
with cryptorchidism	7 (11.1)
without cryptorchidism	56 (88.9)
Iatrogenic	2 (3.1)

3.2. Preoperative results

In total, 177 preoperative complications were identified (mean of 1.6 complications per case, ranging from 0 to 5). The distribution of preoperative complications is summarised in Table 3. 8 (7.2%) patients presented without any complication, 51 (45.9%) had one, 39 (35.1%) had two, 6 (4.5%) had three, 7 (6.3%) had four and 1 (0.9%) had five. Mean length of urethral stenoses was 4.4 cm (median 3.0 cm, range from 0.5 to 15.0 cm). Technical investigations for diagnosing urethral/meatal stenosis were used varyingly: 14 were diagnosed with uroflowmetry alone, 25 with urethrography alone, 3 with urethroscopy alone, 35 with a combination of uroflowmetry and urethrography, 4 with a combination of uroflowmetry and urethroscopy, 1 with a combination of urethrography and urethroscopy and 4 with a combination of all three techniques. 5 stenoses were diagnosed by physical examination only and for 5 stenoses, it was not certain which techniques were used for diagnosis. For 52 surgeries, preoperative urinary flow studies were carried out: the mean Q_{max} was 9.1 ml/s (median 7.9 ml/s, ranging from 1.6 to 22.0 ml/s) and mean voiding volume was 271.6 ml (median 232.5 ml, ranging from 49 to 746 ml). One uroflowmetry just not got the threshold of 50 ml voiding volume and in five, more than 500 ml was voided. However, these uroflowmetry results were included because there was no other uroflowmetry available for these patients. When only including those cases with voiding volumes between 50 and 500 ml, the mean preoperative Q_{max} reached 9.4 ml/s (median 8.4 ml/s, ranging from 2.9 to 20.1 ml/s). The post-void residual urine was known for 14 cases and on average was 84.4 ml (median 50.0 ml, ranging from 0 to 400 ml). Out of 52 patients which were at least once operated for treating urethral and/or meatal stenosis, 19 (36.5%) of them had a history of urinary tract infection before presentation at the tertiary care centre, and an additional 5 (9.6%) of them developed one or more during their course of surgeries.

Table 3. Distribution of preoperative complications (n = 177).

	No. of complications, (%)
Meatal stenosis	32 (18.1)
Urethral stenosis	64 (36.2)
Anterior	4
Penile	29
Posterior	18
Whole length of urethra	9
Not specified	4
Urethrocutaneous fistula	18 (10.2)
Anterior	0
Penile	11
Posterior	6
Not specified	1
Urethral diverticulum	8 (4.5)
Recurrent chordee	13 (7.3)
Glans dehiscence	4 (2.3)
Cosmetic complications	35 (19.8)
Open urethra	2 (1.1)
Abscess	1 (0.6)

For 97 surgeries, it was known if the patient had preoperative functional complaints. In 74 (79.3%), the patient had some degree of functional complaint (fig. 9). 20 patients also filled in an IPSS questionnaire: the mean score was 19.0 (median 20, range from 3 to 35). Of 100 surgeries for which this was available, in 37 (37.0%) the patient preoperatively had some degree of cosmetic complaint (Table 4). Moreover, in 15 (18.1%) of 83 surgeries available for

analysis, there was some degree of sexual complaint: 8 (9.6%) complained about weak or impossible erection and/or ejaculation, 4 (4.8%) had a painful erection and/or penetration, 3 (3.6%) had difficulties with intercourse due to chordee and 2 (2.4%) had no orgasm feeling. Remarkably, the occurrence of any preoperative cosmetic complaint was moderately correlated to the occurrence of any preoperative sexual complaint (Phi coefficient = 0.288, p = 0.009). This correlation was not found between preoperative functional complaints and preoperative cosmetic complaints or between preoperative functional complaints and preoperative sexual complaints.

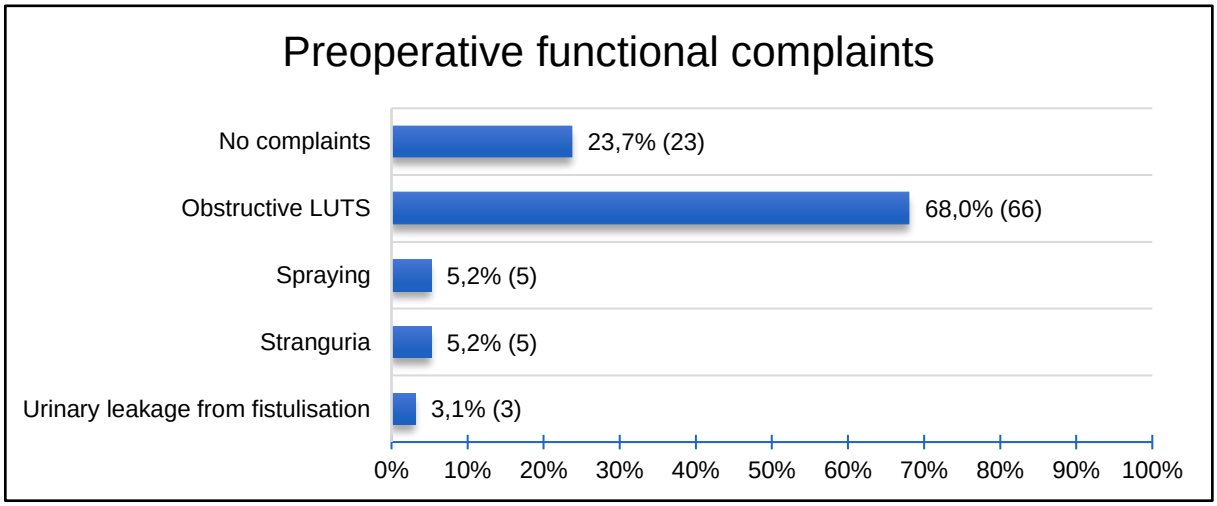


Figure 9. Distribution of preoperative functional complaints (n = 97).

Table 4. Distribution of preoperative cosmetic complaints (n=100).

	No. of complaints, (%)
Urethrocutaneous fistula	18 (18.0)
Unaesthetic scarring	13 (13.0)
Lichen sclerosans	6 (6.0)
Webbing	6 (6.0)
Skin defect	4 (4.0)
Unaesthetic prepuce	2 (2.0)
Unaesthetic circumcision	2 (2.0)
Unaesthetic flap	2 (2.0)
Necrosis	2 (2.0)
Penoscrotal transposition	2 (2.0)
Unaesthetic glans	1 (1.0)
Wide meatus	1 (1.0)
Lymph edema	1 (1.0)

3.3. Surgery results

There were 128 surgical techniques utilised in the 111 surgeries performed. Flap techniques were used 22 (17.2%) times (15 times with penile skin and 7 times with prepuce) while graft techniques with 1-stage BMG were used 20 (15.6%) times. The mean graft length in these surgeries was 6.9 cm (median 5.5 cm, ranging from 2 to 20 cm). During 16 (12.5%) surgeries, a tubularization was performed to construct a neourethra. End-to-end anastomotic techniques and advancement techniques were both used 15 times (11.7%). In 8 (6.3%) surgeries, a non-specific technique for urethrocutaneous fistula closure was utilised and the Sachse urethrotomy technique was used 7 (5.5%) times to open strictures. At the tertiary care centre, there were two different 2-stage techniques utilised for constructing a neourethra: the 2-stage Bracka was used 6 (4.7%) times, while the 2-stage Johanson technique was used 5 (3.9%) times. During 6 (4.7%) surgeries, a perineal urethrostomy was created or revised. Pure aesthetic surgeries were performed 5 (3.9%) times and miscellaneous surgeries were used 3 (2.3%) times. All these procedures were performed by six urologic surgeons with expertise in hypospadias surgery: 44 (39.6%) surgeries were conducted by PH, 41 (36.9%) by WO, 18 (16.2%) by NL, 5 (4.5%) by AV, 2 (1.8%) by EVL and 1 (0.9%) by LAG. 33 (50.8%) of the 65 included patients were circumcised before. 20 (30.8%) patients were additionally circumcised during their course of surgical procedures at the tertiary care centre and 3 (4.6%) patients got a redo circumcision. 4 (6.2%) patients got a preputioplasty, of which one was later circumcised.

3.4. Postoperative results

The mean follow-up period for all patients was 39.4 months (median 20.2) and ranged from 0 to 185.6 months. 4 patients had no consultation anymore after surgery and thus were lost to follow-up, so that conclusions about postoperative complications could not be made. At the surgery level, 39 (36.4%) out of 107 surgeries resulted in no complications and thus could be considered as success. Differentiated according to primary/redo, 4 (57.1%) out of 7 primary surgeries and 35 (35.0%) out of 100 redo surgeries did not result in complications. However, this difference in complication rate was not statistically significant (Fisher's Exact, p = 0.255). Thus, 68 surgeries were followed by 108 complications (Table 5). On average, complications

Table 5. Distribution of postoperative complications (n = 108).

	No. of complications, (%)
Meatal stenosis	13 (12.0)
Urethral stenosis	30 (27.8)
Anterior	5
Penile	12
Posterior	9
Whole length of urethra	1
Not specified	3
Urethrocutaneous fistula	22 (20.4)
Anterior	1
Penile	11
Posterior	8
Not specified	2
Recurrent chordee	2 (1.9)
Cosmetic complications	29 (26.9)
Hematoma	8 (7.4)
Open urethra	1 (0.9)
Abscess	3 (2.8)

originated after 24.8 months (median 6.4 months). Of all complication-related surgeries, 13 (19.1%) of them were followed with early postoperative complications, 28 (41.2%) had short-term complications, 17 (25.0%) had mid-term complications and 10 (14.7%) resulted in long-term complications. In fig. 10, the relationship between the length of follow-up and the occurrence of complications is depicted. Per surgery, a mean of 1.01 complications occurred (median 1 complication, ranging from 0 to 4 complications). One complication occurred after 42 (39.3%) surgeries, two after 15 (14.0%), three after 8 (7.5%) and four after 3 (2.8%). At the patient level, the initial success rate was 36.5% because 23 out of 63 patients (2 patients lost to follow-up after their first surgery) did not develop complications after their first surgery at the tertiary care centre. Differentiated along primary versus redo, the initial success rate was 57.1% (4 out of 7) in primary patients and 33.9% (19 out of 56) in redo patients but there was no statistically significant difference between both groups (Fisher's Exact, p = 0.247). The final patient success rate was 63.9%: 39 out of 61 patients (4 patients lost to follow-up after their last surgery) ended the follow-up period without any complication after their last surgery. 5 (71.4%) out of 7 primary and 34 (63.0%) out of 54 redo cases were successful at the final patient level. Again, the difference in success was not statistically significant (Fisher's Exact, p = 1.00). The course of surgeries for all patients is depicted in fig. 11.

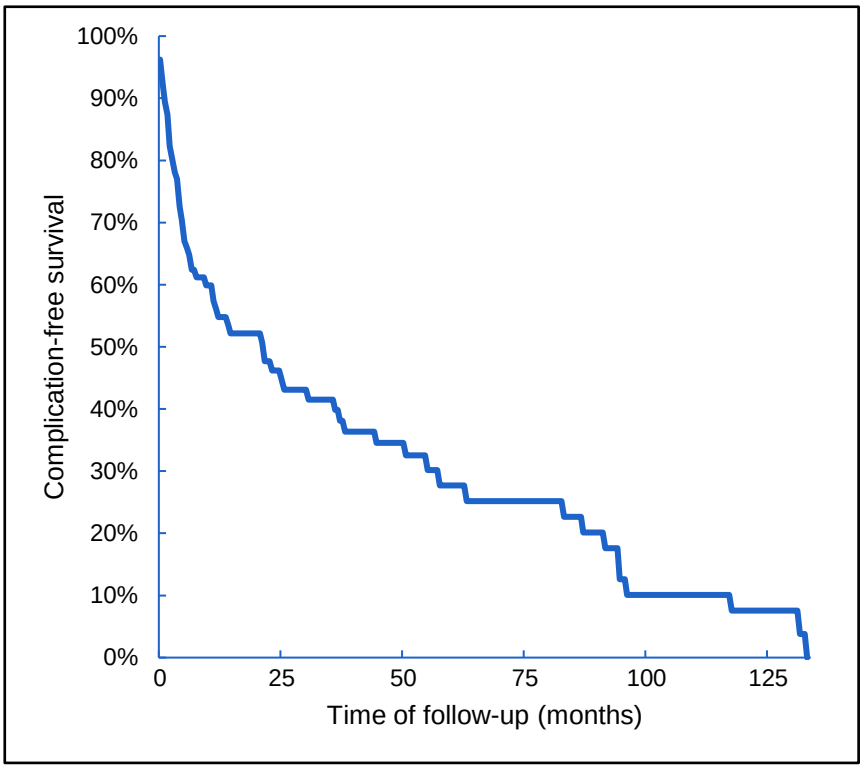


Figure 10. Survival along the time of patients remaining complication free in those surgeries eventually followed by complications.

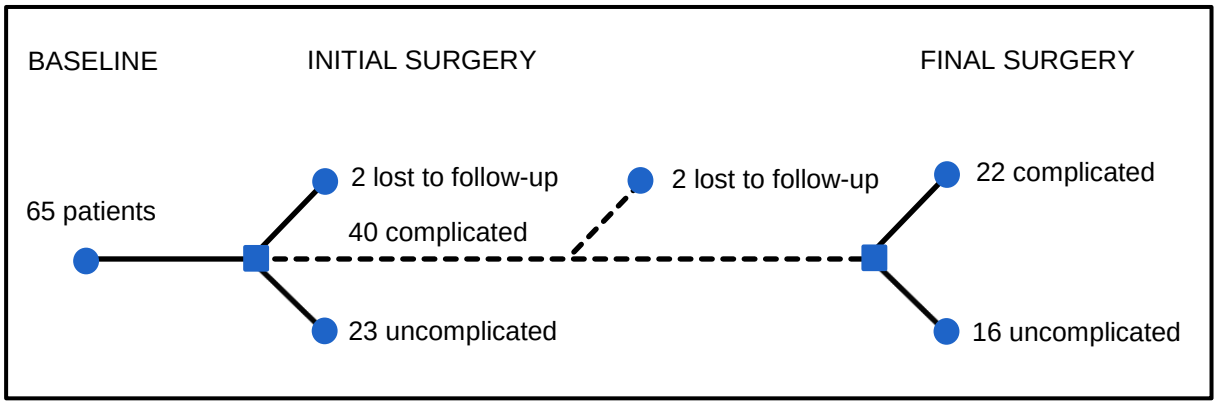


Figure 11. The course of surgeries for all patients. The initial surgery column represents the outcomes of every patient's first surgery conducted at the tertiary care centre. The dotted line represents various additional surgeries for each patient with a complication after first surgery. The final surgery column represents the final outcome of these complicated patients after undergoing their last surgery.

Additionally to the success rate measured above, success rates were also determined by only considering the 'big five' of complications in hypospadias surgery. In this case, the surgery level success rate was 48.6% (52 out of 107 surgeries did not result in one of the 'big five' of complications). For primary surgeries this was 71.4% (success in 5 out of 7 surgeries), while it was 47.0% (success in 47 out of 100) for redo surgeries (Fisher's Exact, p = 0.262). The initial and the final patient level success rate was 49.2% and 80.3%, respectively. This means that 31 out of 63 patients did not develop one of the 'big five' of complications after their first surgery at the tertiary care centre, while 49 out of 61 patients did not develop one of these complications after their last surgery. Primary patients had an initial patient level success rate of 71.4% (5 out of 7) and a final patient level success rate of 85.7% (6 out of 7), while this was 46.4% (26 out of 56) and 79.6% (43 out of 54) for redo patients, respectively. The difference in success rate was not statistically significant neither for the initial (Fisher's Exact, p = 0.257) nor for the final patient level success rate (Fisher's Exact, p = 1.00).

The mean length of postoperative stenoses was 2.0 cm (median 1.0 cm, ranging from 0.5 to 10.0 cm). 8 urethral/meatal stenoses were diagnosed with uroflowmetry alone, 8 with only urethrography, 2 with only urethroscopy, 19 with a combination of uroflowmetry and urethrography, 1 with a combination of uroflowmetry and urethroscopy and 2 with a combination of all three techniques. For 1 stenosis, only physical examination found place and for 2, it was not well documented which techniques were used for diagnosis. Postoperative uroflowmetries were performed in the follow-up of 63 surgeries: mean postoperative Q_{max} was 14.8 ml/s (median 14.4 ml/s, ranging from 3.6 to 35.2 ml/s) and mean voiding volume 270.8 ml (median 239.0 ml, ranging from 90 to 710 ml). In five patients, only uroflowmetries with voiding volumes above 500 ml were available. The mean postoperative Q_{max} was 15.1 ml/s (median 14.4 ml/s, ranging from 3.6 to 35.2 ml/s) when only those uroflowmetries with voiding volumes

between 50 and 500 ml were analysed. Post-void residual urine was assessed in the follow-up of 29 surgeries and on average was 46.6 ml (median 15.0 ml, ranging from 0 to 350 ml). Comparison of pre- and postoperative Q_{max} for uroflowmetries with a voiding volume between 50 and 500 ml revealed very statistically significant differences (Wilcoxon matched-pairs signed-ranks test, p = 0.002) in favour of the postoperative Q_{max}.

In the follow-up of 95 surgeries, data about postoperative functional complaints could be gathered: 43 (45.3%) out of 95 surgeries were associated with postoperative functional complaints (fig. 12). For 19 cases, postoperative IPSS-scores were available: the mean score was 11.7 (median 6) and ranged from 0 to 35. The preoperative IPSS-scores were highly statistically significant different from the postoperative IPSS-scores in favour of the latter (Wilcoxon matched-pairs signed-ranks test, p = 0.028). Out of 98 surgeries available for analysis, 29 (29.6%) were still accompanied with some degree of postoperative cosmetic complaint (Table 6). Similarly, after 17 (20.5%) out of 83 surgeries, the patient had some degree of sexual complaint: in 9 (10.8%), the patient suffered from weak or impossible erections and/or ejaculations, in 4 (4.8%) the patient complained about painful erections and/or penetrations, in 2 (2.4%) the patient had no orgasm feeling, in 1 (1.2%) the patient had troubles with intercourse due to chordee and in 1 (1.2%) the patient had premature ejaculation (*Lat: ejaculation praecox*). Similarly as in the preoperative situation, the occurrence of postoperative functional and cosmetic complaints on one hand, and postoperative functional and sexual complaints on the other hand were not correlated with each other. However, contradictory to the preoperative situation, the occurrence of postoperative cosmetic and sexual complaints were no longer correlated.

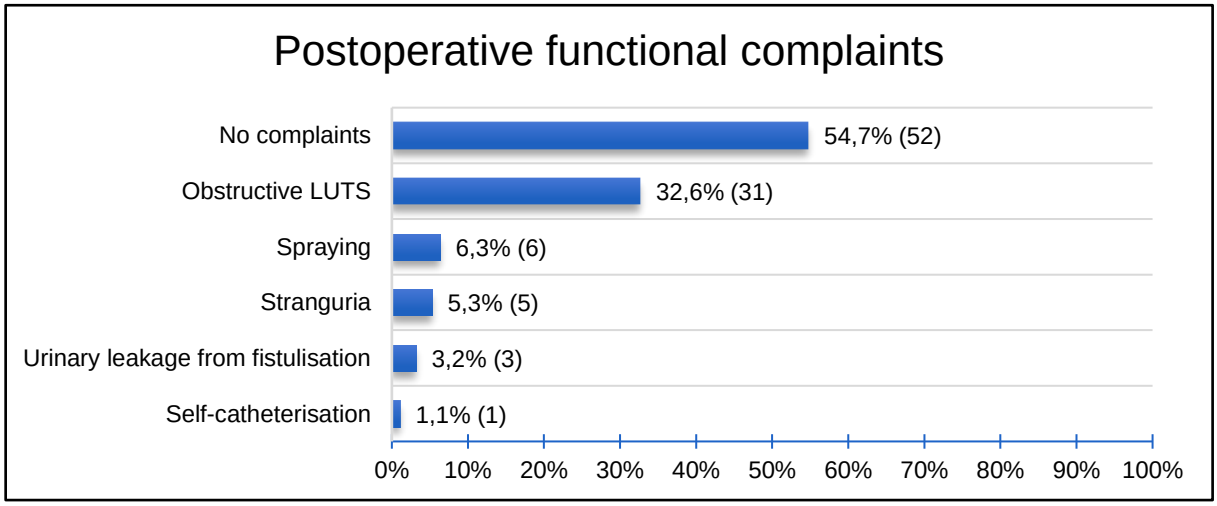


Figure 12. Distribution of postoperative complaints (n = 95).

Table 6. Distribution of postoperative cosmetic complaints (n = 98).

	No. of complaints, (%)
Urethrocutaneous fistula	16 (16.3)
Unaesthetic scarring	5 (5.1)
Lichen sclerosans	5 (5.1)
Skin defect	4 (4.1)
Webbing	3 (3.1)
Necrosis	3 (3.1)
Wide meatus	3 (3.1)
Unaesthetic prepuce	1 (1.0)
Lymph edema	1 (1.0)

There were very statistically significant differences between the occurrence of pre- and postoperative functional complaints (McNemar test, $p < 0.001$). Notably, there were no significant differences between the occurrence of pre- and postoperative cosmetic complaints (McNemar test, $p = 0.868$) nor were there significant differences between the occurrence of pre- and postoperative sexual complaints (McNemar test, $p = 0.774$).

Univariate logistic regression analyses were not able to identify any prognostic factors for developing any postoperative complication, for developing urethral/meatal stenosis or for developing urethrocutaneous fistula.

3.5. Perineal urethrostomy-associated cases

The perineal urethrostomy-associated cases are of particular interest. Out of the 111 surgeries included in this study, 6 (5.4%) were about constructing a perineal urethrostomy after complete failure of hypospadias repair. In 4 of them, the perineal urethrostomy was constructed *de novo*, while in the other 2 a previously constructed perineal urethrostomy was revised because of stenosis. The mean age at *de novo* reconstruction was 56.6 years. Another patient preoperatively had a temporary perineal urethrostomy, after which a flap procedure was performed to construct a patent neourethra with a subcoronal meatus. After the last follow-up visit, 5 (7.7%) out of 65 patients ended up with a perineal urethrostomy of which one of them already had a perineal urethrostomy at first presentation at the tertiary care centre. 4 out of 5 of these patients had congenital hypospadias, while one of them had iatrogenic hypospadias. The latter patient was later diagnosed with metastatic penile squamous cell carcinoma and died at the age of 62 years. One patient presented with an open urethra because of necrosis after a recent surgery for combined meatal and urethral stenosis. The characteristics of these perineal urethrostomy-associated cases are summarized in Table 7.

Table 7. Overview of patients' characteristics associated with perineal urethrostomy.

ID	Aetiology	Age	Meatal location preop	Complication preop	Surgical technique	Meatal location postop
1	Congenital	48.4	Tip of the glans	Urethral stenosis	Perineal urethrostomy	Perineal
2	Congenital	31.3	Perineal urethrostomy	Urethral stenosis	Flap technique	Subcoronal
3	Congenital	39.6	Open urethra	Open urethra (necrosis)	Perineal urethrostomy	Perineal
3	Congenital	44.6	Perineal urethrostomy	Perineal meatal stenosis	Perineal urethrostomy revision	Perineal
4	Congenital	76.5	Penile	Urethral stenosis	Perineal urethrostomy	Perineal
5	Iatrogenic	62.0	Coronal	Urethral stenosis	Perineal urethrostomy, penectomy	Perineal
6	Congenital	63.8	Perineal urethrostomy	Perineal meatal stenosis	Perineal urethrostomy revision	Perineal

4. Discussion

Evaluating outcomes regarding hypospadias surgery remains a challenge because there are no standards of assessment. This is at least partially attributable to the very heterogenous ways in which patients present to the urologist. Also, studies are very heterogeneously designed: various definitions for an 'adult' patient are used, there is no consensus about which complications should be reported and lastly, a variety of definitions for surgical success and failure are in use. For example in this study, the choice was made to define success at both surgery and patient level and *every* complication which occurred was defined as failure, even if the complication resolved spontaneously or could be treated without surgery. As a result of the above mentioned reasons, making comparisons in outcomes between different care centres is difficult. Moreover, outcomes about hypospadias repair in adulthood are scarcely reported in the literature. Nevertheless, in this study, success at the surgery level was 36.4%, meaning that from all surgeries performed for repairing hypospadias in adulthood about two out of five surgeries remain uncomplicated. Although in primary patients the success rate was 57.1% while it was 35.0% in redo patients, this difference was not statistically significant. Looking at the patient level, initial patient success was 36.5% and final patient success was 63.9%, implicating that after the last surgery more than six out of ten patients remain complication-free. Initial and final patient success was again higher in the primary group (57.1% and 71.4%, respectively) than in the redo group (33.9% and 63.0%, respectively) but again, these differences were not statistically significant. The outcomes of other study groups who investigated primary and/or redo hypospadias repair in adulthood for various surgical techniques are summarized in Table 8. Compared to this study, results seem quite inferior to those published in the literature. However, it should be noted that according to best knowledge, this study reported the most different complications of all studies available. Indeed, some studies only focused on urethral complications, so that other non-urethral complications are missed (72-74). Moreover, the mean follow-up period of this study was among the highest and thus more complications could be detected, explaining the relatively low success rate. Also, the mean age of the study group was relatively high compared to other studies: although this has not been proven, some argue that higher age depicts for more complications (75). However, also in this study, age was not found to be a significant risk factor for developing complications. Last but not least, since this study was conducted in a tertiary care centre, challenging cases have been preselected. This is reflected in the fact that numerous patients included in this study were referred by other urologists from other care centres and in the fact that a considerable amount of patients came from other countries. All of the above mentioned reasons, together with other methodologic factors already discussed earlier, are able to clarify the outcomes of this study compared to those available in the literature.

Table 8. Summary of reports regarding hypospadias repair in adults.

Author	Mean follow-up, mean age at repair	Study population	Level of success	Success (%)
Snodgrass, 2014 (76) (subgroup analysis)	15 months, 23 years	Primary (n=8) adult patients Redo (n=61) adult patients Total (n=69)	Surgery level[1] Surgery level[1] Surgery level[1]	87.5[3] 73.8[3] 75.4
Myers, 2012 (72)	89 months (median), 38 years	Redo adult patients (n=50, 74 surgeries performed)	Initial patient level Final patient level	50 76
Dodson, 2007 (77)	14 months, 13 years	Primary adult patients (n=31)	Surgery level[1]	52
Barbagli, 2006 (64)	33.8 months, 32.2 years	Redo adult patients (n=60)	Final patient level	75
Adayener, 2006 (75)*	19 months, 21.8 years	Primary adult patients (n=80) Redo adult patients (n=17) Total (n=97)	Surgery level[1] Surgery level[1] Surgery level[1]	91.3[2] 76.5[2] 88
Senkul, 2002 (73)	28 months, 21.9 years	Primary adult patients (n=59) Redo adult patients (n=29) Total (n=88) 	Initial patient level Final patient level Initial patient level Final patient level Initial patient level Final patient level	89.8[4] 96.6[4] 72.4[4] 89.7[4] 84.1 94.3
Hensle, 2001 (74)	1-228 months (range), 22.5 years	Primary adult patients (n=8) Redo adult patients (n=34) Total (n=42) 	Initial patient level Final patient level Initial patient level Final patient level Initial patient level Final patient level	62.5[4] 100[4] 44.1[4] 85.3[4] 47.6 88.1

** Only distal hypospadias cases. [1]Because every patient underwent one surgery, the surgery level outcome was identical to the initial and final patient level outcome. [2]Significant difference. [3]No significant difference. [4]Statistical comparisons were not made.*

In order to make comparisons with other studies more relevant, the outcomes for the 'big five' of complications were analysed separately. Here, it was observed that the surgery level success rate was 48.6%, while the initial and final patient level success rate was 49.2% and 80.3%, respectively. Because Snodgrass et al. (76) only reported the 'big five' of complications, comparisons with this study can be more adequately made. Although the results of this study remain inferior compared to those published by Snodgrass et al. (76), comparisons with other studies, which reported more or less similar complications as the 'big five', show analogue outcomes (64, 72, 77). However, it still should be recognized that comparing outcomes remains extremely difficult.

The role of already having undergone penile surgeries before (i.e. being a redo patient) in predicting complications is also unclear in the literature: the study of Adayener et al. (75) found significantly better success rate in primary patients than in redo patients (75), while in the study of Snodgrass et al. (76), the better success rate for primary patients was not significantly different from the success rate in redo patients (76). Also in the present study, outcomes for primary patients were not significantly different compared to outcomes for redo patients. The insignificance is potentially a consequence of the small sample size of primary patients in both this study as in the one from Snodgrass et al. (76).

For the same reasons as mentioned above, comparing outcomes between studies which investigate paediatric patients and studies which investigate adult patients is difficult. However, outcomes of hypospadias repair in primary paediatric patients have recently been published for this tertiary care centre. In this study, 474 primary patients undergoing a total of 628 surgeries were analysed. Tubularization techniques were used in 39.9% of the primary repairs, advancement techniques in 36.1% and flap techniques in 17.3% of the primary surgeries. In 5.3%, other techniques were used. The surgery level success rate was 64.1% (not published). The initial patient success rate after primary repair was 75.9%. For the other 24.1% of patients additional repairs were needed. The main complications which occurred necessitating redo surgery were fistulas (46.4%), cosmetic complications (31.3%) and meatal stenosis (28.6%). After undergoing all additional repairs required, the final success rate rose up to 84.4% (not published) (78, 79). Thus, comparison of the success rate between children and adults reflects that adult patients who need additional repair for hypospadias belong to the most difficult and challenging subgroup of hypospadias patients to treat. Trends in the use of surgical techniques demonstrate that flap- and graft-assisted procedures are relatively more used in the adult setting than in the paediatric setting, while tubularization techniques and advancement techniques become relatively less important. This is a logical consequence of the fact that adult patients, with a history of multiple failed repairs, have scarce locally available healthy tissue for constructing a neourethra and thus alternative tissues need to be implemented. When

comparing the kind of complications which occur, it seems that stenotic complications are more important findings in adulthood than in childhood while urethrocutaneous fistulas are relatively less important, although it remains an important reason for surgical failure. Remarkably, cosmetic concerns already come along after the first failed surgery and stay more or less constant in importance throughout adulthood.

The study of Snodgrass et al. (76) is the only study available which directly compares the outcomes of paediatric and adult patients in both primary and redo repair. They concluded that there are no differences in complication rate between paediatric and adult patients, both in the primary and redo setting (76). These findings are contradictory to the one's presented above and probably again reflect the considerable heterogeneity which is present in adult hypospadias patients.

As demonstrated in fig. 10, a great part of complications occur early after surgery. However, a significant amount of complications occur after more than five years and one case was only followed by a complication after more than eleven years. Thus, in order to determine the valid complication rate, it is mandatory to assure long-term follow-up for hypospadias patients, since late complications are not unfrequently seen.

Unfortunately, it was not possible to identify any prognostic factors for surgical outcome. Although the retrospective design of this study certainly could have influenced these analyses, these findings probably indicate once more that adult hypospadias patients are a very heterogenous group of patients. Parallel to analyses of the paediatric population of primary patients of this tertiary care centre, only proximal hypospadias was identified as a significant predictor for re-intervention (79).

One of the strengths of this study is that functional, cosmetic and sexual complaints are systematically reported both pre- and postoperatively. The results demonstrate that patients notably complain about the urinating function of the penis, while cosmetic and sexual complaints are reported in a lesser extent. Remarkably, the occurrence of cosmetic and sexual complaints was moderately associated with each other in the preoperative situation. This should implicate that when a patient complains about penile cosmesis, the caregiver should also ask about sexual function and vice versa. However, in the postoperative situation, this association disappeared, so it is unclear if this finding is a veritable one. Comparison of the pre- and the postoperative status illustrate that surgery is mainly able to handle functional complaints of patients: there were significant fewer patients with postoperative functional complaints in comparison with preoperative functional complaints. Also, despite the low sample size for which this analysis was available, the IPSS was significantly better postoperatively (mean score of 11.7) than preoperatively (mean score of 19.0). On the other

hand, surgery was not able to clearly improve the cosmetic and sexual complaints of patients. This is an important finding that should be communicated with the patient, namely that surgery especially is capable of dealing with functional complaints, but that certainties about cosmesis and sexual function cannot be given. However, it should be noticed that these results are possibly an underestimation of the reality. Especially for sexual complaints, patients can feel ashamed to report about this topic. Caregivers can also feel uncomfortable asking about patients' sexual function. Therefore, it is possible that these complaints are underreported. Moreover, reporting about complaints is subjective and prone to interindividual heterogeneity. Both of these issues could be addressed with questionnaires: in this manner, the hindering to report about personal problems is reduced and complaints are more objectively inventoried. For this study, a small subgroup of patients filled in an IPSS, making objective assessments about functional obstructive complaints possible. Although this questionnaire is able to identify the biggest part of functional complaints which occur in hypospadias patients, others like spraying are missed. Thus, a functional questionnaire specifically designed for hypospadias patients and covering all of these complaints should be created. Also, although some argue that its value is modest (3), urinary flow studies should preferably be taken into account so that one overriding scoring system for evaluating hypospadias patients' functional status could be used. Cosmetic satisfaction is more objectively assessed with the HOPE (Hypospadias Objective Penile Evaluation)-score (80) (see appendix 2) and the PPS (Penile Perception Score) (see appendix 3) (81). Both have their advantages and disadvantages: the HOPE-score has the advantage of having a good intra- and interobserver reliability, probably because it provides reference pictures for evaluating cosmesis. However, the downside of this scoring system is that is has only been validated for evaluation by surgeons (80). Although the PPS has the advantage it has been designed for evaluation by both surgeon and patient, interobserver reliability is poor (81). Because these questionnaires have been developed recently, they could not yet be implicated in this outcome-study. Finally, sexual function can be more objectively addressed with the International Index of Erectile Function (IIEF)-score, a widely used scoring system which assesses sexual desire, erectile function, orgasmic function and intercourse satisfaction (82). Unfortunately, the IIEF could not be assessed in this study. Although these questionnaires offer great added value in outcome reporting, one should not forget that a well-taken anamnesis and asking about patients' satisfaction remain crucial elements in a constructive doctor-patient relationship. Therefore, questionnaires should be seen as a complementary measure rather than seeing it as a substitute.

In clinical practice, the creation of a perineal urethrostomy is a temporary or definite solution to complex urethral problems. The temporary use of this urethrostomy makes it possible for patients to void independently while awaiting further reconstructive surgery for urethral, mainly

stenotic, complications. However, some patients who have already undergone multiple failed reconstructive urethroplasties are literally ‘tired’ of dealing with the uncertainties they have to cope with when opting for another reconstructive attempt. For those patients, providing a definite solution is relieving. Although perineal urethrostomies can also fail, this solution is generally more easily accepted because revision is quickly done with high success rates. Moreover, creation of a perineal urethrostomy is far less invasive than undergoing a complex urethroplasty. Based on a report, 70% of all procedures performed for creating a perineal urethrostomy were successful, while 30% failed. Despite this, patients who opted for this solution were satisfied or very satisfied in more than 95% of the cases. Subgroup analysis of those who underwent a perineal urethrostomy-procedure after failed hypospadias repair even revealed that all patients were satisfied or very satisfied. Moreover, it seemed that patients who underwent this procedure for failed hypospadias repair had higher success rates up to 87.5%, although this was not statistically confirmed (60).

This study has several limitations to cope with. First of all, this study had a retrospective design and thus not all of the information for every patient was available. Especially for meatal location, it was rarely clear where the meatus was positioned preoperatively. As already discussed above, it was not completely possible to assess outcomes in an objective manner, nor was it possible to systematically determine outcomes with standardized questionnaires, except for a subgroup of patients which filled in an IPSS. Therefore, complaints were subjectively assessed and prone to bias. Another aspect which imposes to interpret the results of this study with caution, is that patients not returning for follow-up visit after initial success are always interpreted as surgical success on long-term. For example, patients with complications could confront barriers to revisit the caregiver with their problems or they could be treated elsewhere in a secondary care centre. As a consequence, success rates are potentially estimated too optimistically. Theoretically, follow-up visits should be planned on a fixed basis to determine the real complication-rate. However, this is not practically achievable and too expensive. Moreover, all of the study designs are confronted with this same issue. Another limitation is that psychosocial aspects of patient satisfaction, for example relationship satisfaction, could not be assessed while psychosexual aspects, for example negative genital appraisal, were evaluated too superficially to obtain a truthful image. The fact that outcomes of multiple surgeons were included made it possible to rule out outcome bias produced by the specific practices, habits and activities of a single surgeon which could have influenced the outcome. This should therefore not be seen as a limitation. To conclude, although the results of this study should be interpreted with caution, it was demonstrated that adult hypospadias patients undergoing primary or redo repair are at greater risk of developing complications in comparison with children. This finding is relevant for clinical practice, especially because adult

patients opting to undergo surgical repair can be counselled based on scientific data, so that they are able to make informed decisions and to make a personal balance of potential benefits and risks of the procedure.

As already extensively discussed above, there is a demanding need to standardize evaluation of outcomes. Although standardizing outcomes is complicated because of the interindividual heterogeneity, efforts should be made to provide a more consistent way of reporting. Only by doing so, caregivers and researchers will be able to reliably compare results between different surgical techniques, patient groups, care centres and so on. As already mentioned above, the HOPE-score and the PPS both reflect the progress in this standardization process (80, 81). The Hypospadias Objective Scoring Evaluation (HOSE) is another tool that has been developed to objectively evaluate outcomes of hypospadias surgery. It is a five-point scoring system assessing meatal location, meatal shape, urinary stream, occurrence of curvature during erection and occurrence of fistula. It thus combines functional, cosmetic and sexual elements to determine outcome. Advantages of this scoring system include its clinical usefulness, its good reproducibility and its ease of use because its measurement solely relies on clinical examination. However, its use for research purposes is insufficient: a lot of complications other than fistula are not assessed, other important cosmetic concerns are missed and sexual function is evaluated too superficially (83) (see appendix 4). To conclude, the HOSE reflects the ongoing trend of standardization in hypospadias outcome reporting, but on its own is insufficient. Also, in this study, attempts were made to more systematically report surgical outcomes. Concepts like ‘surgery level success’, ‘initial patient level success’ and ‘final patient level success’ were introduced in order to facilitate the standardization process of outcome reporting. Although satisfactory standardization probably will be a long-term achievement, following recommendations which can be readily implemented into future research are made:

- Means on how outcomes were determined should be systematically reported;
- An unambiguous definition of success and/or failure should be described;
- It should be clear which complications are reported and especially, those which are not. As recommended in an expert panel consensus, complications which should always be reported include meatal stenosis, urethral stenosis, fistula, glans dehiscence and diverticula (3);
- The mean age at surgery and mean follow-up time should be consistently reported;
- Preferably, complications should be subdivided into early postoperative, short-term, midterm and long-term complications (71).

More research in the field of hypospadias surgery is required. Well-designed prospective studies with standardized approaches to classification, diagnosis, treatment and objective outcome assessment are needed in order to achieve more evidence based medicine in hypospadias surgery.

5. Conclusions

Despite the fact that comparisons of outcomes of hypospadias surgery should be interpreted with caution, it was shown that adult patients undergoing hypospadias surgery for primary repair or for treatment of surgical complications are at greater risk of developing complications in comparison with children. Prognostic factors could not be identified, reflecting the high amount of interindividual heterogeneity in these patients. Long-term follow-up is advised since late complications are not unfrequently seen. Standardization of outcome-evaluation and -reporting is necessary to reliably compare results between different surgical techniques, different patient groups and different care centres.

6. Reference list

1. Schoenwolf GC, Bleyl SB, Brauer PR, Francis-West PH. Development of External Genitalia. In: Hyde M, Gruliow R, editors. Human Embryology. fourth ed 2009. p. 521-35.
2. Mouriquand PDE, Demède D, Gorduza D, Mure P-Y. Hypospadias. Pediatric Urology (Second Edition). Philadelphia: W.B. Saunders; 2010. p. 526-43.
3. Snodgrass W, Macedo A, Hoebeke P, Mouriquand PD. Hypospadias dilemmas: a round table. J Pediatr Urol. 2011;7(2):145-57.
4. Hoebeke P, Van Laecke E, De Boe V, Groen LA. Kinderurologie. In: Hoebeke P, Michielsen D, De Wachter S, editors. Urologie: Uitgeverij Academia Press; 2017. p. 17-48.
5. Kraft KH, Shukla AR, Canning DA. Hypospadias. Urol Clin North Am. 2010;37(2):167-81.
6. Harris P, Merer DM, Palmer LS, Menasse-Palmer L. Hypospadias. In: Bernstein D, Shelov SP, editors. Pediatrics1996. p. 324-6.
7. van der Zanden LF, van Rooij IA, Feitz WF, Franke B, Knoers NV, Roeleveld N. Aetiology of hypospadias: a systematic review of genes and environment. Hum Reprod Update. 2012;18(3):260-83.
8. Natali A. Tipi di ipospadia (Classificazione): Alessandro Natali; [cited 2016 8 November]. Available from: www.profnatali.it.
9. Tekgül S, Dogan HS, Hoebeke P, Kocvara R, Nijman JM, Radmayr C, et al. Paediatric Urology Guidelines: European Association of Urology; [cited 2016 8 November]. Available from: http://uroweb.org/guideline/paediatric-urology/#1.
10. Orkiszewski M. A standardized classification of hypospadias. J Pediatr Urol. 2012;8(4):410-4.
11. Malone P. Commentary to "A standardized classification of hypospadias". J Pediatr Urol. 2012;8(4):415.
12. Springer A, van den Heijkant M, Baumann S. Worldwide prevalence of hypospadias. J Pediatr Urol. 2016;12(3):152 e1-7.
13. Kraft KH, Shukla AR, Canning DA. Proximal hypospadias. ScientificWorldJournal. 2011;11:894-906.
14. Yamada G, Satoh Y, Baskin LS, Cunha GR. Cellular and molecular mechanisms of development of the external genitalia. Differentiation: International Society of Differentiation; 2003.
15. Schoenwolf GC, Bleyl SB, Brauer PR, Francis-West PH. Larsen's Human Embryology, 4th Edition. Churchill Livingstone; 2008.
16. Hutson JM. Cryptorchidism and Hypospadias. In: De Groot LJ, Chrousos G, Dungan K, Feingold KR, Grossman A, Hershman JM, et al., editors. Endotext. South Dartmouth (MA)2000.
17. Li Y, Sinclair A, Cao M, Shen J, Choudhry S, Botta S, et al. Canalization of the urethral plate precedes fusion of the urethral folds during male penile urethral development: the double zipper hypothesis. J Urol. 2015;193(4):1353-59.
18. D'herde K. Ontwikkeling van het Genitaal Stelsel. Blok 4 Voortplanting en Seksualiteit: Embryologie en Anatomie 2015. p. 59-69.
19. Kurzrock EA, Baskin LS, Cunha GR. Ontogeny of the male urethra: theory of endodermal differentiation. Differentiation. 1999;64(2):115-22.
20. Hadidi AT, Roessler J, Coerdt W. Development of the human male urethra: a histochemical study on human embryos. J Pediatr Surg. 2014;49(7):1146-52.
21. Montag S, Palmer LS. Abnormalities of penile curvature: chordee and penile torsion. ScientificWorldJournal. 2011;11:1470-8.
22. Chen MJ, Macias CG, Gunn SK, Dietrich JE, Roth DR, Schlomer BJ, et al. Intrauterine growth restriction and hypospadias: is there a connection? Int J Pediatr Endocrinol. 2014;2014(1):20.
23. Kalfa N, Philibert P, Sultan C. Is hypospadias a genetic, endocrine or environmental disease, or still an unexplained malformation? Int J Androl. 2009;32(3):187-97.
24. Fredell L, Kockum I, Hansson E, Holmner S, Lundquist L, Lackgren G, et al. Heredity of hypospadias and the significance of low birth weight. J Urol. 2002;167(3):1423-7.
25. Kalfa N, Philibert P, Baskin LS, Sultan C. Hypospadias: interactions between environment and genetics. Mol Cell Endocrinol. 2011;335(2):89-95.
26. Hiort O. Long-term management of patients with disorders of sex development (DSD). Ann Endocrinol (Paris). 2014;75(2):64-6.
27. Hughes I. How should we classify intersex disorders? J Pediatr Urol. 2010;6(5):447-8.
28. Thankamony A, Lek N, Carroll D, Williams M, Dunger DB, Acerini CL, et al. Anogenital distance and penile length in infants with hypospadias or cryptorchidism: comparison with normative data. Environ Health Perspect. 2014;122(2):207-11.

29. Hsieh MH, Eisenberg ML, Hittelman AB, Wilson JM, Tasian GE, Baskin LS. Caucasian male infants and boys with hypospadias exhibit reduced anogenital distance. Hum Reprod. 2012;27(6):1577-80.
30. Klip H, Verloop J, van Gool JD, Koster ME, Burger CW, van Leeuwen FE, et al. Hypospadias in sons of women exposed to diethylstilbestrol in utero: a cohort study. Lancet. 2002;359(9312):1102-7.
31. Carbone P, Giordano F, Nori F, Mantovani A, Taruscio D, Lauria L, et al. The possible role of endocrine disrupting chemicals in the aetiology of cryptorchidism and hypospadias: a population-based case-control study in rural Sicily. Int J Androl. 2007;30(1):3-13.
32. Beleza-Meireles A, Omrani D, Kockum I, Frisen L, Lagerstedt K, Nordenskjold A. Polymorphisms of estrogen receptor beta gene are associated with hypospadias. J Endocrinol Invest. 2006;29(1):5-10.
33. Urology Care Foundation. How is hypospadias treated? : Urology Care Foundation; 2005 [cited 2016 8 November]. Available from: www.urologyhealth.org.
34. Peretz D, Westreich M. Pseudo-iatrogenic hypospadias: the megameatus intact-prepuce hypospadias variant. Plast Reconstr Surg. 2003;111(3):1182-5.
35. Kliegman RM, Jenson HB, Marcdante KJ, Behrman RE. Anomalies of the Penis. In: Schmitt W, Mahon J, editors. Nelson Essentials of Pediatrics. 5th ed. p. 767-70.
36. Jacobsen AS, Dator D, Torres CM, Florentino A, Tekgul S, Yoshino K, et al. Pediatric Varicocele, Micropenis, Buried and Webbed Penis, Penile Torsion, Diphallia, Penoscrotal Transposition, and Aphallia. In: deVries CR, Nijman R, editors. Congenital Anomalies in Children. Vancouver: Société Internationale d'Urologie; 2013. p. 177-216.
37. Bhat A. General considerations in hypospadias surgery. Indian J Urol. 2008;24(2):188-94.
38. Aigrain Y, Cheikhelard A, Lottmann H, Lortat-Jacob S. Hypospadias: surgery and complications. Horm Res Paediatr. 2010;74(3):218-22.
39. Perlmutter AE, Morabito R, Tarry WF. Impact of patient age on distal hypospadias repair: a surgical perspective. Urology. 2006;68(3):648-51.
40. Subramaniam R, Spinoit AF, Hoebeke P. Hypospadias repair: an overview of the actual techniques. Semin Plast Surg. 2011;25(3):206-12.
41. Malik RD, Liu DB. Survey of pediatric urologists on the preoperative use of testosterone in the surgical correction of hypospadias. J Pediatr Urol. 2014;10(5):840-3.
42. Netto JM, Ferrarez CE, Schindler Leal AA, Tucci S, Jr., Gomes CA, Barroso U, Jr. Hormone therapy in hypospadias surgery: a systematic review. J Pediatr Urol. 2013;9(6 Pt B):971-9.
43. Wright I, Cole E, Farrokhyar F, Pemberton J, Lorenzo AJ, Braga LH. Effect of preoperative hormonal stimulation on postoperative complication rates after proximal hypospadias repair: a systematic review. J Urol. 2013;190(2):652-59.
44. Gorduza DB, Gay CL, de Mattos ESE, Demede D, Hameury F, Berthiller J, et al. Does androgen stimulation prior to hypospadias surgery increase the rate of healing complications? - A preliminary report. J Pediatr Urol. 2011;7(2):158-61.
45. Baskin LS, Hinman FJ. Vascularized Flaps for Hypospadias Repair. In: Djordjevic ML, editor. Hypospadias Surgery: Challenges and Limits. New York: Nova Science Publishers, Inc.; 2014. p. 83-100.
46. Snodgrass W, Bush N. Tubularized Incised Plate for Distal and Proximal Primary Hypospadias Repair. In: Djordjevic ML, editor. Hypospadias Surgery: Challenges and Limits. New York: Nova Science Publishers, Inc.; 2014. p. 65-82.
47. Bar Yosef Y, Binyamini J, Matzkin H, Ben-Chaim J. Midline dorsal plication technique for penile curvature repair. J Urol. 2004;172(4 Pt 1):1368-9.
48. Jednak R, Hernandez N, Spencer Barthold J, Gonzalez R. Correcting chordee without hypospadias and with deficient ventral skin: a new technique. BJU Int. 2001;87(6):528-30.
49. Snodgrass W, Yucel S. Tubularized incised plate for mid shaft and proximal hypospadias repair. J Urol. 2007;177(2):698-702.
50. Snodgrass WT. Tubularized incised plate hypospadias repair: indications, technique, and complications. Urology. 1999;54(1):6-11.
51. Hofer MD, Han JS, Gonzalez CM. Full-Thickness Skin Grafts for Hypospadias Repair. In: Djordjevic ML, editor. Hypospadias Surgery: Challenges and Limits. New York: Nova Science Publishers, Inc.; 2014. p. 101-18.
52. Djordjevic ML, Stojanovic B. Combined Flaps and Grafts Urethroplasty in Severe Hypospadias Repair. In: Djordjevic ML, editor. Hypospadias Surgery: Challenges and Limits. New York: Nova Science Publishers, Inc.; 2014. p. 149-60.

53. McLorie G, Joyner B, Herz D, McCallum J, Bagli D, Merguerian P, et al. A prospective randomized clinical trial to evaluate methods of postoperative care of hypospadias. J Urol. 2001;165(5):1669-72.
54. Van Savage JG, Palanca LG, Slaughenhoupt BL. A prospective randomized trial of dressings versus no dressings for hypospadias repair. J Urol. 2000;164(3 Pt 2):981-3.
55. Hakim S, Merguerian PA, Rabinowitz R, Shortliffe LD, McKenna PH. Outcome analysis of the modified Mathieu hypospadias repair: comparison of stented and unstented repairs. J Urol. 1996;156(2 Pt 2):836-8.
56. Springer A, Krois W, Horcher E. Trends in hypospadias surgery: results of a worldwide survey. Eur Urol. 2011;60(6):1184-9.
57. Kojovic VL, Bizic MR, Djordjevic ML. Non-Urethral Complications after Hypospadias Repair. In: Djordjevic ML, editor. Hypospadias Surgery: Challenges and Limits. New York: Nova Science Publishers, Inc.; 2014. p. 179-96.
58. Al-Salem A. Hypospadias. An Illustrated Guide to Pediatric Surgery. Switzerland: Springer International Publishing; 2014. p. 545-57.
59. Palminteri E, Berdondini E, Di Pierro GB. Urethral Reconstruction after Failed Hypospadias Repair. In: Djordjevic ML, editor. Hypospadias Surgery: Challenges and Limits. New York: Nova Science Publishers, Inc.; 2014. p. 161-78.
60. Barbagli G, De Angelis M, Romano G, Lazzeri M. Clinical outcome and quality of life assessment in patients treated with perineal urethrostomy for anterior urethral stricture disease. J Urol. 2009;182(2):548-57.
61. Djakovic N, Kuehhas FE. Hypospadias: Anatomy and Etiology. In: Djordjevic ML, editor. Hypospadias Surgery: Challenges and Limits. New York: Nova Science Publishers, Inc.; 2014. p. 1-10.
62. Bhat A, Bhat M, Kumar V, Kumar R, Mittal R, Saksena G. Comparison of variables affecting the surgical outcomes of tubularized incised plate urethroplasty in adult and pediatric hypospadias. J Pediatr Urol. 2016;12(2):108 e1-7.
63. Hatipoglu NK, Bodakci MN, Soylemez H, Sancaktutar AA, Atar M, Penbegul N, et al. Tubularized incised plate repair in circumcised adults. Med Glas (Zenica). 2013;10(2):316-20.
64. Barbagli G, De Angelis M, Palminteri E, Lazzeri M. Failed hypospadias repair presenting in adults. Eur Urol. 2006;49(5):887-94; discussion 95.
65. Eswara JR, Geminiani J, Brandes SB. Hypospadias Cripple: Challenges and Limits. In: Djordjevic ML, editor. Hypospadias Surgery: Challenges and Limits. New York: Nova Science Publishers, Inc.; 2014. p. 197-212.
66. Andrews HO, Nauth-Misir R, Shah PJ. Iatrogenic hypospadias--a preventable injury? Spinal Cord. 1998;36(3):177-80.
67. Garg G, Baghele V, Chawla N, Gogia A, Kakar A. Unusual complication of prolonged indwelling urinary catheter - iatrogenic hypospadias. J Family Med Prim Care. 2016;5(2):493-4.
68. Snodgrass WT. Assessing outcomes of hypospadias surgery. J Urol. 2005;174(3):816-7.
69. Gonzalez R, Ludwikowski BM. Importance of urinary flow studies after hypospadias repair: a systematic review. Int J Urol. 2011;18(11):757-61.
70. Barry MJ, Fowler FJ, Jr., O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. J Urol. 1992;148(5):1549-57; discussion 64.
71. Nuininga JE, RP DEG, Verschuren R, Feitz WF. Long-term outcome of different types of 1-stage hypospadias repair. J Urol. 2005;174(4 Pt 2):1544-8; discussion 8.
72. Myers JB, McAninch JW, Erickson BA, Breyer BN. Treatment of adults with complications from previous hypospadias surgery. J Urol. 2012;188(2):459-63.
73. Senkul T, Karademir K, Iseri C, Erden D, Baykal K, Adayener C. Hypospadias in adults. Urology. 2002;60(6):1059-62.
74. Hensle TW, Tennenbaum SY, Reiley EA, Pollard J. Hypospadias repair in adults: adventures and misadventures. J Urol. 2001;165(1):77-9.
75. Adayener C, Akyol I. Distal hypospadias repair in adults: the results of 97 cases. Urol Int. 2006;76(3):247-51.
76. Snodgrass W, Villanueva C, Bush N. Primary and reoperative hypospadias repair in adults--are results different than in children? J Urol. 2014;192(6):1730-3.
77. Dodson JL, Baird AD, Baker LA, Docimo SG, Mathews RI. Outcomes of delayed hypospadias repair: implications for decision making. J Urol. 2007;178(1):278-81.
78. Spinoit AF, Poelaert F, Groen LA, Van Laecke E, Hoebeke P. Hypospadias repair at a tertiary care center: long-term followup is mandatory to determine the real complication rate. J Urol. 2013;189(6):2276-81.

79. Spinoit AF, Poelaert F, Van Praet C, Groen LA, Van Laecke E, Hoebeke P. Grade of hypospadias is the only factor predicting for re-intervention after primary hypospadias repair: a multivariate analysis from a cohort of 474 patients. J Pediatr Urol. 2015;11(2):70 e1-6.
80. van der Toorn F, de Jong TP, de Gier RP, Callewaert PR, van der Horst EH, Steffens MG, et al. Introducing the HOPE (Hypospadias Objective Penile Evaluation)-score: a validation study of an objective scoring system for evaluating cosmetic appearance in hypospadias patients. J Pediatr Urol. 2013;9(6 Pt B):1006-16.
81. Weber DM, Landolt MA, Gobet R, Kalisch M, Greeff NK. The Penile Perception Score: an instrument enabling evaluation by surgeons and patient self-assessment after hypospadias repair. J Urol. 2013;189(1):189-93.
82. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology. 1997;49(6):822-30.
83. Holland AJ, Smith GH, Ross FI, Cass DT. HOSE: an objective scoring system for evaluating the results of hypospadias surgery. BJU Int. 2001;88(3):255-8.
84. Royal United Hospitals Bath NHS Foundation Trust. International prostate symptom score (IPSS): Royal United Hospitals Bath NHS Foundation Trust; 2017 [cited 2017 11 November]. Available from: http://www.ruh.nhs.uk/patients/Urology/documents/patient_leaflets/Form_IPSS.pdf.
85. Nederlands Huisartsen Genootschap. Vragenlijst voor plasklachten bij mannen (IPSS): Nederlands Huisartsen Genootschap; 2013 [cited 2017 11 November]. Available from: https://www.hammershuisartsen.nl/files/vragenlijst_plasklachten.pdf.
86. Weber DM, Schonbucher VB, Landolt MA, Gobet R. The Pediatric Penile Perception Score: an instrument for patient self-assessment and surgeon evaluation after hypospadias repair. J Urol. 2008;180(3):1080-4; discussion 4.

7. Appendix

Appendix 1: IPSS questionnaire

English version

Over the past month:	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always
…how often have you had a sensation of not emptying your bladder completely after you finish urinating?	0	1	2	3	4	5
…how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5
…how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
…how difficult have you found it to postpone urination?	0	1	2	3	4	5
…how often have you had a weak urinary stream?	0	1	2	3	4	5
…how often have you had to push or strain to begin urination?	0	1	2	3	4	5
…how many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning?	0x	1x	2x	3x	4x	5x

Table based on (84).

Dutch version

Hoe vaak in de afgelopen maand:	Nooit	Minder dan 1 op 5 keer	Minder dan de helft van de keren	Ongeveer de helft van de keren	Meer dan de helft van de keren	Bijna altijd
…had u het gevoel dat uw blaas na het plassen nog niet helemaal leeg was?	0	1	2	3	4	5
…moest u binnen twee uur na het plassen opnieuw plassen?	0	1	2	3	4	5
…gebeurde het tijdens het plassen dat de straal enige keren stopte en dan weer begon?	0	1	2	3	4	5
…had u moeite om het plassen uit te stellen?	0	1	2	3	4	5
…had u een slappe straal bij het plassen?	0	1	2	3	4	5
…moest u persen voordat de urinestraal op gang kwam?	0	1	2	3	4	5
…moest u gemiddeld per nacht het bed uit om te plassen?	0x	1x	2x	3x	4x	5x

Tabel gebaseerd op (85).

Appendix 2: HOPE questionnaire

1. **Position meatus:** assess the position of the meatus?
    a. Position 1 — 10 points
    b. Position 2 — 8 points
    c. Position 3 — 5 points
    d. Position 4 — 3 points
    e. Position 5 — 1 point
2. **Shape meatus:** what is the shape of the meatus?
    a. Normal — 10 points
    b. Slightly abnormal — 7 points
    c. Moderately abnormal — 4 points
    d. Severely abnormal — 1 point
3. **Shape glans:** what is the shape of the glans?
    a. Normal — 10 points
    b. Slightly abnormal — 7 points
    c. Moderately abnormal — 4 points
    d. Severely abnormal — 1 point
4. **Shape skin**: what is the shape of the penile skin?
    a. Normal — 10 points
    b. Slightly abnormal — 7 points
    c. Moderately abnormal — 4 points
    d. Severely abnormal — 1 point
5. **Torsion:** is there a torsion of the penis?
    a. 0-30° — 10 points
    b. 30-50° — 7 points
    c. 50-70° — 4 points
    d. >70° — 1 point
6. **Curvature in penile erection:** is there a curvature of the penis in erection?
    a. No erection observed — question 6 does not account for the HOPE-score
    b. 0-30° — 10 points
    c. 30-50° — 7 points
    d. 50-70° — 4 points
    e. >70° — 1 point

Hypospadias Objective Penile Evaluation (HOPE)-score = mean number of points question 1-6.

Questionnaire reprinted from (80) (reference pictures not included in this appendix).

Appendix 3: PPS questionnaire

The chart below shows various aspects about your penis. There are four possible answers: very satisfied, satisfied, dissatisfied, very dissatisfied. Please mark with a cross the box that corresponds best.

	Very satisfied	Satisfied	Dissatisfied	Very dissatisfied
Penile length	□(3)	□(2)	□(1)	□(0)
Position and shape of the urethral opening	□(3)	□(2)	□(1)	□(0)
Shape of the glans	□(3)	□(2)	□(1)	□(0)
Shape of the penile skin	□(3)	□(2)	□(1)	□(0)
Penile axis (straightness upon erection)	□(3)	□(2)	□(1)	□(0)
General appearance of the penis	□(3)	□(2)	□(1)	□(0)

Reprinted from (86).

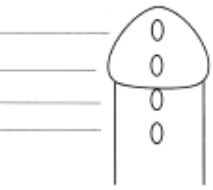
Appendix 4: HOSE questionnaire

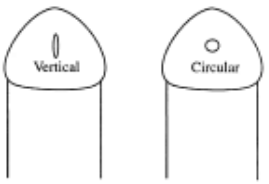
HOSE - Hypospadias Objective Scoring Evaluation

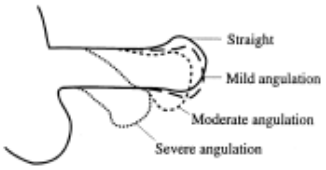
Assessor: **Patient:**

Date:

Variable	Score	Diagram
1. Meatal location		
Distal glanular	4	
Proximal glanular	3	
Coronal	2	
Penile shaft	1	
2. Meatal Shape		
Vertical slit	2	
Circular	1	
3. Urinary Stream		
Single stream	2	
Spray	1	
4. Erection		
Straight	4	
Mild angulation (< 10^{o})	3	
Moderate angulation (> 10^{o} but < 45^{o})	2	
Severe angulation (> 45^{o})	1	
5. Fistula		
None	4	
Single - subcoronal or more distal	3	
Single - proximal	2	
Multiple or complex	1	
Total		







Reprinted from (83).